ORAL PRESENTATIONS

NEURO-IMAGING I

O.01. INFLUENCE OF P-GLYCOPROTEIN Expression ON 99mTc-TETROFOSSM IN UPTAKE IN GLIOMAS

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OBJECTIVE: Multidrug resistance (MDR) remains a major obstacle to successful chemotherapeutic treatment of cancer and can be caused by overexpression of P-glycoprotein, the MDR1 gene product. P-glycoprotein (P-gp) recognizes several chemotherapeutic agents as a substrate and prevents their accumulation. Among them, both technetium-99-sestamibi and technetium-99-tetrofosmin (99mTc-TF) are single photon emission computed tomography tracers. 99mTc-MIBI uptake has been proven in vitro and in vivo to inversely correlate with P-gp levels of tumors. In vitro studies have shown that 99mTc-TF is influenced in a lesser degree from the P-gp expression, thus may be superior to 99mTc-MIBI for brain tumor imaging. In the present study, we evaluated in vivo whether 99mTc-TF uptake correlates with P-gp levels in gliomas.

MATERIALS AND METHODS: Eighteen patients (10 males, 8 females, mean age 57.3 years) with histologically confirmed glioma were included in the study. There were 13 glioblastoma multiforme cases, 2 anaplastic astrocytomas, 2 anaplastic oligodendrogliomas, and 1 low grade astrocytoma. Brain SPECT by 99mTc-TF was performed within a week prior to surgical excision and the expression of P-gp was assessed by immunohistochemistry. Radiotracer accumulation was assessed by a semiquantitative method of image analysis, calculating the lesion-to-normal (L/N) uptake ratio. RESULTS: The tracer uptake ranged from faint to profound (mean L/N = 8.2, range 1.8-20). The P-gp expression ranged from 0% to 45%. Using Spearman’s rho analysis we found no correlation between tracer uptake (L/N) and P-gp expression in gliomas. Our data suggest that 99mTc-TF uptake is not influenced by P-gp expression in gliomas. Thus, 99mTc-TF constitute a suitable radiotracer for gliomas imaging.

CONCLUSION: pMRI seems to be a reliable technique to distinguish PD from Ps-PD in patients with recurrent GBM, and these results deserve further testing in larger sample for confirmation.

O.03. ASSESSMENT OF BEVACIZUMAB/IRINOTECAN RESPONSE IN MALIGNANT GLIOMA BY ADC MAP IMAGE ANALYSIS

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BACKGROUND: Response assessment in malignant glioma following antiangiogenic treatment is challenging for conventional MR imaging (MRI). Despite decreased contrast-enhancement, non-enhancing parts of the tumor may continue to grow. In this retrospective study, we analyzed patients with recurrent malignant glioma during Bevacizumab/irinotecan therapy using ADC map image analysis from diffusion-weighted MRI to yield ultrastructural information on cellular density and properties of the extracellular matrix in relation to the progression-free survival.

METHODS: Fifteen patients treated with Bevacizumab/irinotecan for recurrent malignant glioma were investigated by MRI every 2–3 months until tumor progression. Applying image segmentation, volumes of contrast-enhanced lesions on T1 and hyperintense non-enhancing T2 lesions were calculated. T2 hyperintense lesions were defined as regions of interest (ROIs) and registered to the corresponding ADC maps (T2-ADC). Histograms and cumulative histograms of the T2-ADC ROIs were calculated to quantify the apparent gray scale value distribution and were compared with progression-free survival. Software tools were used to perform segmentation (ITK-Snap), calculation of T2-ADC histograms (Imagej), and statistical figures (SPSS).

RESULTS: At 3-month follow-up, the overall mean contrast-enhanced T1 volume (in cm3) decreased significantly from 263 (± 29.43) at pre-treatment to 140.95 (± 50.94) to 203.22 (± 126.52). According to Macdonald criteria, 12 patients showed response and 3 patients progressed. During the same period of time, the mean T2 volume (in cm3) was significantly reduced in 8 cases (P = .005) from 127.32 (± 59.01) to 85.61 (± 42.12) and increased in 7 cases (P = .08) from 140.95 (± 50.94) to 203.22 (± 126.52). T2-ADC cumulative histograms showed differences in terms of gradient and kurtosis. In 8 cases an increasing gradient and high kurtosis represented an increased amount of low ADC grey scale values that can be interpreted as an augmentation of cellular density of the tumor. These patients showed a lower chance of progression-free survival compared with patients (n = 6) with a decreasing slope and low kurtosis of the T2-ADC cumulative histograms. CONCLUSION: Changes in grey scale distribution in ADC cumulative histograms in patients with malignant recurrent glioma may be predictive for antiangiogenic treatment response.

O.04. RADIOGRAPHIC PATTERNS OF RELAPSE IN Glioblastoma

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BACKGROUND: Glioblastoma (GBM) is defined pathologically as an infiltrative glioma, and salvage therapy with bevacizumab is believed to increase the incidence of diffuse and distant invasion as assessed radiographically. PATIENTS AND METHODS: 80 adult patients with glioblastoma multiforme (GBM) following chemoradiation were evaluated for radiographic progression from pseudo-progression (Ps-PD). At first recurrence, 80 patients were treated with single agent, bevacizumab. At time of progression, 57 patients were treated with bevacizumab and a cytotoxic chemotherapy, cytotoxic chemotherapy alone, or on an investigational trial. Magnetic resonance imaging (MRI) were analyzed at four time points in each patient: at presentation, at first, second, and third recurrence. Four patterns of radiographic disease were assessed, local (unifocal disease), distant (second lesion noncontiguous with primary lesion), multifocal (>2 lesions including leptomeningeal dissemination), and diffuse. RESULTS: At presentation, 87.5% of glioblastoma were local, 6.25% distant, 3.75% multifocal, and 2.5% diffuse. At first recurrence following progression on RT/TMZ and before initiation of bevacizumab, 80% were local, 7.5% distant, 6.25% multifocal (including 1 with CSF dissemination), and 6.25% diffuse. At second recurrence following progression on bevacizumab, 71.25% were local, 8.75% distant, 8.75% multifocal (2 of 7 with CSF dissemination), and 11.25% were diffuse. At third recurrence (57 patients evaluable), 71.25% were local, 7.0% distant, 7.0% multifocal, and 14.0% were diffuse. Survival following progression on bevacizumab did not differ by pattern of radiographic recurrence. CONCLUSION: A majority of adult patients with GBM at diagnosis manifest MRI-defined local disease and maintain this pattern notwithstanding multiple recurrences and treatment with bevacizumab.
GLIOBLASTOMA MULTIFORME AND ANAPLASTIC GLIOMA

O.05. PREOPERATIVE ESTIMATION OF EXTENT OF RESECTION OF GLIOMAS BY DTI-FTI

D.T.I.-fiber tracking (DTI-FTI) allows the reconstruction of subcortical tracts and their relationship with tumors. This work assesses the ability of preoperative DTI-FTI to predict the extent of resection achievable during surgery of gliomas performed with intraoperative brain mapping. A total of 220 patients with gliomas (mostly low grade) were included. In all patients, the corticospinal tract (CST), the intermediate fronto-occipital (IFO), and superior longitudinalis (SLF) fasciculi were reconstructed by DTI-FTI. The relationship of each of the tracts (CST, IFO, and SLF) with the tumor mass was scored by two independent observers as being unchanged, dislocated, or infiltrated. Intratraqueal protocol included intratraqueal language and motor mapping and monitoring (EEG, EvG, EMG, and MEP). DTI-FTI images were loaded into the neuronavigation system and available during surgery. Surgery was carried out according to functional boundaries. For each patient, preoperative and postoperative MR images and DTI-FTI were loaded into the neuronavigation software and image fusion was used to evaluate the extent of resection as well as the correlation between the resection boundaries and the preoperative DTI-FTI. A correlation between the preoperative score of each tract and the extent of resection (scored on FLAIR volumetric images) was then investigated. Most of the tracts were inside and infiltrated by the tumor (80%); 40% of the tumor showed more than one tract infiltration. The infiltration of the tract varied according to the extent of resection but was less than 50% in 50% of the cases on the average, which decreased to 45% and to 33% when 2 or 3 tracts were involved, respectively. The involvement of CST and IFO were more frequently associated with a reduced chance of resection. Preoperative estimation in DTI-FTI of the level of CST and IFO were better correlated with the extent of resection than CST and IFO, which is the chance of performing a total resection. When CST and IFO are infiltrated by the tumor, a total removal is rarely possible; when outside, an extensive resection is feasible. Preoperative DTI-FTI identifies those patients who will mostly benefit from surgery.

O.06. USEFULNESS OF MET-PET, FLT-PET, AND FMISO-PET FOR SURGICAL TREATMENT OF GLIOMAS

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OBJECTIVE: L-[Methyl-11C]methionine (MET) positron emission tomography (PET), [11C]fluoro-2-deoxy-2-fluoromethyl-D-glucose (FDG) PET, and [18F]-fluoromisonidazole (FMISO) are sensitive modalities for visualizing proliferation, brain tumor, and tumor hypoxia. The objectives of this study were to evaluate the relationships between the uptake of MET, FLT, or FMISO and the histopathological grading in gliomas. METHODS: We examined 51 patients (22 males, 29 females; mean age: 48.7 years; range: 2–89 years; 10 diffuse astrocytomas, 1 oligodendroglioma, 5 anaplastic astrocytomas, 11 glioblastomas, 1 oligoastrocytoma, 18 glioblastomas) using MET–PET, FLT–PET, and FMISO–PET. Finally, 10 patients (6 males, 4 females; mean age: 55.8 years; range: 30–72 years; 1 diffuse astrocytoma, 2 anaplastic astrocytomas, 7 glioblastomas) were examined with FMISO–PET. MET, FLT, and FMISO uptakes were assessed by standardized uptake value of the tumor showing the maximum uptake (SUmean), and the ratio of tumor tissue to the contralateral normal gray matter (T/N ratio). The tumor activity and degree of malignancy were evaluated using Ki-67 index. The correlations between SUVmean and Ki-67 index were determined. RESULTS: All glioblastomas showed tumor uptake of MET, FLT, and FMISO. The difference in MET/T/N ratio was statistically significant between grades II and IV gliomas, but not significant between grades II and III gliomas. The difference in FLT/T/N ratio was statistically significant between grades III and IV gliomas, but not significant between grades II and III gliomas. The difference in FMISO/T/N ratio was statistically significant between grades III and IV gliomas. FLT SUmean in the tumor had a stronger correlation with Ki-67 index than MET SUmean. CONCLUSIONS: PET studies using MET, FLT, and FMISO are useful for preoperative diagnosis in gliomas. FLT–PET seems to be superior to MET–PET in assessment of the proliferation activity on gliomas of different grades. FMISO–PET is useful for non-invasive assessment of hypoxia in malignant gliomas. Advances in molecular imaging such as PET imaging techniques will facilitate more safe and solid management and therapy for the patients with malignant gliomas.

O.07. MGMT PROMOTER METHYLATION STATUS AND EXPRESSION OF DNA MISMATCH REPAIR GENES IN PAIRED PRIMARY AND RECURRENT GLOBLASTOMA: A RETROSPECTIVAL STUDY OF THE GERMAN GLIOMA NETWORK

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INTRODUCTION: Hypermethylation of the MGMT promoter is strongly associated with longer progression-free and overall survival in glioblastoma (GBM) patients treated with radiotherapy and concomitant and adjuvant chemotherapy. We here addressed the question whether GBM relapses are associated with changes in the MGMT promoter methylation status or altered expression of the DNA mismatch repair genes MLH1, MSH2, MSH6, or/and PM2. METHODS: MGMT promoter methylation status was determined in primary and recurrent brain tumors using nonquantitative methylaton-specific PCR (MSP). The vital tumor cell content of each primary and recurrent tumor specimen was histologically determined. Quantitative promoter methylation analyses using DNA pyrosequenencing of MGMT in 48 patients as well as the DNA mismatch repair genes MLH1, MSH2, MSH6, and PM2 in 42 patients. Furthermore, the levels of MGMT, MLH1, MSH2, MSH6, and PMS2 proteins were analyzed semiquantitatively by immunohistochemistry (IHC) in 43 patients. RESULTS: MSP revealed MGMT promoter hypermethylation in 27 patients, borderine methylation in 3 patients, and no methylation in 50 patients at diagnosis. In 73 of the 80 patients, the MGMT promoter status of the primary tumor was retained at recurrence. In 6 patients, loss or reduction of MGMT promoter methylation were detected in the recurrent tumor; however, in 3 patients, this finding was explained by low tumor cell contents in the recurrent tumor specimens. In 1 patient, a change from MGMT borderline methylation (8% methylated alleles) to hypermethylation (50% methylated alleles) was detected. None of the investigated primary and recurrent glioblastomas showed MLH1, MSH2, MSH6, or PMS2 promoter hyperhypermethylation. However, immunohistochemical expression scores for MLH1, MSH2, MSH6, and PMS2 proteins were frequently reduced in the recurrent tumor when compared with the corresponding primary tumor. CONCLUSION: The MGMT promoter methylation status does not change from the primary to the recurrent tumor in the vast majority of GBM patients. Accordingly, changes in the MGMT promoter methylation status are unlikely to account for acquired resistance to temozolomide. Our results further suggest that GBM recurrences often demonstrate lower MLH1, MSH2, MSH6, and/or PMS2 immunoreactivity scores. However, MLH1, MSH2, MSH6, and PMS2 promoter hypermethylation does not appear to account for these decreased protein levels and is not linked to GBM recurrence. Accordingly, the changes in the MGMT promoter methylation status are unlikely to account for acquired resistance to temozolomide.

O.08. MGMT mRNA TRANSCRIPTIONAL ACTIVITY PREDICTS CLINICAL OUTCOME IN MALIGNANT GLIOMAS AFTER RADIO-/CHEMOTHERAPY

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OBJECTIVE: Epigenetic silencing of the gene that encodes for O6-methylguanine-DNA-methyltransferase (MGMT) has been correlated with favorable clinical outcome in patients with malignant gliomas after radio-/chemotherapy using alkylating agents such as temozolomide; it has been hypothesized that MGMT promoter methylation leads to a decreased MGMT mRNA transcriptional activity and subsequent protein expression with a diminished ability of the tumor to repair chemotherapy-induced lesions. The real clinical impact of this assumption, however, is still remains controversial. In the current prospective study, we analyzed the predictive impact of MGMT mRNA expression in malignant glioma (64 patients) after radiotherapy and/or chemotherapy with temozolomide and its correlation with the MGMT promoter methylation status. METHODS: Only vital tumor samples harvested from open...
O.09. UPDATED RESPONSE ASSESSMENT CRITERIA FOR HIGH-GRADE GLIOMAS (HGG): REPORT FROM THE RESPONSE ASSESSMENT IN NEURO-ONCOLOGY (RANO) WORKING GROUP

M. van den Bent 1, D. MacDonald 2, S. Chang 3, M. A. Vogelbaum 4, and P. Y. Wen 1; 1Daniel den Hoed Cancer Center, Rotterdam, Netherlands; 2London Regional Cancer Center, London, ON, Canada; 3UCSF, San Francisco, CA; 4Cleveland Clinic, Cleveland, OH; 5Dana Farber/Carei Chemotherapy in Patients with Recurrent GBM: A Prospective, Randomized, Open Label, Phase III Clinical Trial of NovoTTF-100A vs Best Standard of Care. RESULTS: Histopathological diagnosis revealed 54 glioblastoma multiforme and 10 anaplastic astrocytomas. Thirty-two tumors were methylated and 32 tumors exhibited a low MGMT transcriptional activity (cut-off value: 0.45), respectively. Low MGMT mRNA expression turned out to be a strong predictive factor for PFS, OS, and Favorable TR in univariate and multivariate models (P < .0001); even though the degree of MGMT mRNA expression strongly correlated with the methylation status (P < .0001), discordant findings were seen in 30% of the patients: Patients with a methylated tumor and high MGMT mRNA expression (15%) did significantly worse than those with low transcriptional activity (P < .001). Conversely, uncorrected tumors with low MGMT mRNA expression (15% of the unmethylated tumors) did better than their counterparts. CONCLUSION: Determination of MGMT mRNA expression is a powerful method for predictive evaluation of malignant gliomas. A substantial rate of discordant findings elucidates the fact that treatment decision in favor of chemotherapy with alkylating agents should not be based on the MGMT methylation status alone.

O.10. A PROSPECTIVE, RANDOMIZED, OPEN LABEL, PHASE III CLINICAL TRIAL OF NOVOTT-100A VS BEST STANDARD OF CARE CHEMOTHERAPY IN PATIENTS WITH RECURRENT GILOBLASTOMA

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BACKGROUND: The NovoTTF-100A device is a portable, home use, medical device which delivers low intensity, intermediate frequency, alternating electric fields (TTFFields) to the brain by means of non-invasive, disposable scalp electrodes. TTFFields physically interfere with cell division and assembly of organelles (Kirsch et al. Cancer, 2004; Kirson et al. Proc Natl Acad Sci USA, 2007; Salzberg et al. Onkologie, 2008 Kirson et al. BMC Med. Phys. 2009). METHODS: Adult patients with recurrent GBM were to be randomized (1:1) to either NovoTTF-100A administered continuously (20–24 hours/day, 7 day/week) or the best local standard of care (BSC) chemotherapy, at the physicians discretion, in each center. Randomization was stratified by prior surgery for recurrence and center. The number of prior treatments was not limited; a Karnofsky performance status of ≥ 70% and an adequate end-organ function were required. The primary endpoint was overall survival; secondary endpoints included 1-y survival, PFS, TTP, radiological response rate and safety. The study was powered to detect a 60% increase in overall survival (eg, 48 vs 30 weeks) with a two-sided type I error rate of 0.05 and power of 0.80. RESULTS: Between September 2006 and May 2009, 237 patients were included in 28 centers in the United States, Europe, and Israel, 120 patients were treated with NovoTTF-100A alone, and 117 patients received BSC chemotherapies including bevacizumab, nitrosoureas, procarbazine, or PCV combination. Overall survival (OS) was analyzed by real-time qPCR and normalized against adequate house-keeping genes. Primary endpoint was progression-free survival (PFS). Secondary endpoints were overall survival (OS) and treatment response (TR). RESULTS: Histopathological diagnosis revealed 54 glioblastoma multiforme and 10 anaplastic astrocytomas. Thirty-two tumors were methylated and 32 tumors exhibited a low MGMT transcriptional activity (cut-off value: 0.45), respectively. Low MGMT mRNA expression turned out to be a strong predictive factor for PFS, OS, and Favorable TR in univariate and multivariate models (P < .0001); even though the degree of MGMT mRNA expression strongly correlated with the methylation status (P < .0001), discordant findings were seen in 30% of the patients: Patients with a methylated tumor and high MGMT mRNA expression (15%) did significantly worse than those with low transcriptional activity (P < .001). Conversely, uncorrected tumors with low MGMT mRNA expression (15% of the unmethylated tumors) did better than their counterparts. CONCLUSION: Determination of MGMT mRNA expression is a powerful method for predictive evaluation of malignant gliomas. A substantial rate of discordant findings elucidates the fact that treatment decision in favor of chemotherapy with alkylating agents should not be based on the MGMT methylation status alone.

O.11. STEM/PROGENITOR CELL FLEXIBILITY DETERMINES BOTH NORMAL BRAIN DEVELOPMENT AND BRAIN TUMORS

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How the programming and reprogramming of stem/progenitor cells regulate normal brain development and brain cancer is still not well known. One of the tools that we have chosen to investigate stem/progenitor cell regulation is the neuronal transcriptional repressor, REI-silencing transcription factor (REST). REST is expressed in most neuronal cells, including neural progenitor cells (NSCs), but is absent in most neuronal cells. Previously, we found that countering REST function by forced activation of REST target genes in NSCs, and even muscle progenitor cells, was sufficient to cause neuronal differentiation of NSCs, and even muscle progenitor cells. Although REST is normally not expressed in most neuronal cells, we previously found that approximately 50% of human medulloblastomas, a malignant pediatric brain tumor, express REST and that this abnormal expression of REST causes medulloblastoma-like cerebellar tumors by maintaining “stemness” of NSCs. We then found that REST maintains self-renewal and pluripotency in ES cells and this process is regulated by extracellular matrix components. Our recent work indicates that REST regulates self-renewal of normal NSCs and its expression is diminished as NSCs differentiate. Interestingly, a subset of glioblastoma patient sample-derived cancer-initiating cells (glioblastoma stem-like cells or GSCs) expresses abnormal levels of REST. The role of REST in the GSCs is to maintain stemness through a microRNA-mediated mechanism. We are currently working on examining whether REST could function as a therapeutic target in these glioblastoma tumors. Taken together, the results of our studies indicate that stem/progenitor cells are more flexible than previously believed and that simple alteration of transcriptional regulators in these cells can affect both normal brain development and brain tumors, such as glioblastoma.
O.12. EFFICIENT ENGRAFTMENT OF MGMP140K GENE-MODIFIED CD34+ CELLS FOLLOWING NONMYELOABLATIVE BCNU CONDITIONING IN PATIENTS WITH GLIOBLASTOMA

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BACKGROUND: Glioblastoma, the most common adult primary malignant brain tumor, confers poor prognosis (median survival of 15 months) notwithstanding aggressive treatment. Combination chemotherapy including carmustine (BCNU) or temozolomide (TMZ) with the MGMT inhibitor O6-benzylguanine (O6BG) has been used, but has associated with dose-limiting hematotoxicity. OBJECTIVE: To assess safety and efficacy of a retroviral vector encoding the O6BG-resistant MGMP140K gene for transduction and autologous transplantation of hematopoietic stem cells (HSCs) in MGMT unmethylated, newly diagnosed glioblastoma patients in an attempt to chemopotentiate bone marrow during combination O6BG/TMZ therapy. METHODS: Three patients have been enrolled in the first cohort. Patients underwent standard radiation therapy without TMZ followed by G-CSF mobilization, apheresis, and conditioning with 600 mg/m² BCNU prior to infusion of gene-modified cells. Posttransplant, patients were treated with 28-day cycles of single dose TMZ (472 mg/m²) with 48-hour intravenous O6BG (120 mg/m²), then 30 mg/m²/d. RESULTS: The BCNU dose was nonmyeloablative with ANC < 500/μL for ≤ 3 d and nadir thrombocytopenia of 28,000/μL. Gene marking in pre-infusion colony forming units (CFUs) ranged from 28.5% to 47.4%. Patients have received 1 and 2 cycles of O6BG/TMZ, respectively, with evidence for selection of gene-modified cells. One patient has received a single-dose-escalated cycle at 590 mg/m² TMZ. No additional hematotoxicity has been observed thus far and all three patients exhibit stable disease at ≥ 8 months subsequent DG-PCR analysis. We believe that these data demonstrate the feasibility of achieving significant engraftment of MGMP140K-modified cells with a well-tolerated dose of BCNU. Further follow-up will determine whether this approach will allow for further dose escalation of TMZ and improved survival.

MOLECULAR MARKERS I

O.13. MOLECULAR MALIGNANT PROGRESSION IN GLIOMAS: ELUCIDATING THEIR GENETIC “LIFE STORY”

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Up till now, typing and grading of diffuse gliomas is based on histopathological features. However, because of, especially, lack of unequivocal criteria and sampling, the robustness of this classification is suboptimal, and more objective tools are needed for more reliable assessment of their biological behavior (eg, nearly all low-grade diffuse gliomas eventually progress to high-grade malignancy); however, time to progression varies considerably and there is currently no valid parameter that unambiguously predicts how rapidly malignant progression will occur. Over the last decades it has become increasingly clear that molecular genetic markers are helpful in recognizing more uniform subgroups of gliomas (eg, loss of chromosome 1p and 19q is reported to predict longer survival and better response to chemotherapy whereas methylation of the MGMT gene predicts chemosensitivity to alkylating agents). Furthermore, several genes were reported to be involved in malignant progression of gliomas; however, detailed information about their “timing” and cooccurrence in the course of malignant progression is relatively lacking. We therefore evaluated in a spectrum of over 300 diffuse gliomas the co-occurrence of copy number changes involving chromosomes 1p and 19q, CDKN2A, PTEN, and EGFR(VIII) as detected by MS-PCR, with reproducibilities of 72% and 7%, respectively. A good linearity was observed for each technique (after sequential mixing of 100% and 0% Meth). MethyLight (P = .001 for cut off 9%), MS-PCR (P < .0001), and IHC (P < .001/cut off 25%). MethyLight (P = .09) and MS-HRM (P = .03) yielded disappointing results in this series of patients. Contrary to recent studies, MGMT expression assessed by IHC was well correlated with overall survival. As observer variability is a reported problem with this technique, which could account for the poor reproducibility observed in this study, stained slides are currently evaluated by 2 other pathologists to validate the result. For MGMT promoter methylation analysis, PYR appears to be a very robust technique and a good alternative to classical MS-PCR, which is not well adapted to clinical practice. The next step of the project aims at implementing these techniques in different laboratories.

O.14. COMPARISON OF MS-PCR, METHYLIGHT, PYROSEQUENCING, MGMT IMMUNOHISTOCHEMISTRY FOR MGMT ANALYSIS

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1CRLCC (mean 31%) in 1 case and from 3% to 20% (mean 8%) in the other. MS-PCR (P = .001) and MS-HRM yielded similar results in this study, stained slides are currently evaluated by 2 other pathological to validate the result. For MGMT promoter methylation analysis, PYR appears to be a very robust technique and a good alternative to classical MS-PCR, which is not well adapted to clinical practice. The next step of the project aims at implementing these techniques in different laboratories.

O.15. TRANSCRIPTIONAL INACTIVATION AND PROMOTER HYPERMETHYLATION OF THE TUMOR SUPPRESSOR GENE NDRG2 IN HIGH-GRADE OLIGODENDROGLIAL TUMORS

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BACKGROUND: The NDRG2 gene is a member of the N-myc downstream-regulated gene family that is located on chromosome 14q11.2. It has been proposed that the NDRG2 gene is a candidate tumor suppressor gene (TSG), which is highly methylated in leukemia and breast cancer and promotes cell differentiation. Consistent with its potential function as a TSG, downregulation

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O.17. EXPRESSION OF TELOMERASE REVERSE TRANSCRIPTASE (hTERT) IN HUMAN GLOBLASTOMA SPECIMENS IS ASSOCIATED WITH SHORTER PATIENT SURVIVAL AND IS A PREREQUISITE FOR IN VITRO IMMORTALIZATION

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A comparison of human glioma clinical samples with cell lines and xenografts revealed that hTERT is a key component for glioma cell immortalization. To clarify the role of hTERT in glioma aggressiveness we investigated the expression patterns of hTERT in human biopsy samples, cell lines, primary cultures, and xenografts. hTERT expression was detected in all gliomas and the respective cell lines, whereas none of the xenografts displayed hTERT. Lack of hTERT expression was associated with aggressive biological behavior and lower survival rates. These results suggest the potential of hTERT as a prognostic tool for glioma aggressiveness.
Abstracts

O.19. PROSPECTIVE MULTICENTRIC VALIDATION OF A SURVIVAL PROGNOSTIC INDEX IN LEPTOMENINGEAL CARCINOMATOSIS: ANALYSIS INTERIM OF THE ACME STUDY

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INTRODUCTION: Leptomeningeal carcinoma of the CNS (LC) represents a devastating complication of systemic cancer. Although median survival is short despite therapy, up to 10–20% of patients can achieve 1-year survival with treatment. To decide which patients should be treated is difficult. To help in the decision of which patients are best candidates to be treated, a survival prognostic index (PI) was recently proposed. The ACME study is conducted to validate this PI. The aim of this report is to present the preliminary results. PATIENTS AND METHODS: The enrolment was initiated on June 2008 and recruitment period will finish on June 2010, participating 29 Spanish centers. LC diagnosis is based on the presence of positive cytology on cerebrospinal fluid (CSF) or CSF biochemical abnormalities associated with suggestive clinical and magnetic resonance. Clinical data, CSF parameters, tumor-related characteristics, and treatment information are recorded. PI is composed by 3 prognostic variables: Radiation Therapy Oncology Group (RTOG) neurological scale ≤2, glucose level in CSF ≥2.7 mmol/L, and presence of infratentorial symptoms. Each variable is scored as 0 or 1, according to the absence or presence. Group of unfavorable PI includes patients who score ≥2 points. The impact of single parameters on overall survival is determined by both univariate and multivariate analysis. RESULTS: Up to now, 73 patients are enrolled. Data from the first 46 patients included with complete follow-up was analyzed. Thirty-four patients received intrathecal with or without systemic chemotherapy. Univariate analysis identified female sex, breast cancer, Karnofsky Performance Status, negative CSF cytology, PI, and treatment (intrathecal with or without systemic chemotherapy) as prognostic influence on survival. However, multivariate analysis revealed that breast cancer (HR: 3.03; 95% CI: 1.18–7.69, P=.021), negative CSF cytology (HR: 3.85; 95% CI: 1.33–11.11, P=.012), treatment (HR: 7.14; 95% CI: 2.5–20, P<.001), and PI (HR: 2.77; 95% CI: 1.1–7.14, P=.031) were associated independently with longer overall survival in LC patients. CONCLUSION: Preliminary results confirm PI as useful prognostic score in LC patients. Moreover, breast cancer and a negative cytology on CSF also emerge as independent good prognostic factors.

O.20. NEOPLASTIC MENINGITIS: VALUE OF MRI AND PROTEIN ANALYSIS AND PATTERNS OF LYMPHOMATOUS CYTOMORPHOLOGY

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INTRODUCTION: Neoplastic meningitis (NM) from lymphoma or leukemia, although a well-known and relatively frequent complication of aggressive lymphoma and leukemia, is still difficult to detect. With cytology, one key diagnostic procedure, neurolymphocytes are difficult to distinguish from inflammatory lymphocytes. We evaluated here whether specific morphological criteria can improve this differentiation. Moreover, we assessed the sensitivity of MRI and protein analysis for the detection of all kinds of NM in comparison with CSF cytology.

O.21. CASE SERIES OF FRAMELESS LINEAR ACCELERATOR-BASED STEREOTACTIC RADIOSURGERY TO THE POSTOPERATIVE RESECTION CAVITY FOR BRAIN METASTASIS: AN INITIAL REPORT OF OUTCOMES AND PATTERNS OF FAILURE

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BACKGROUND: Whole-brain radiotherapy (WBRT) is the standard of care following resection of a brain metastasis. Lack of a survival benefit and concern regarding possible neurocognitive effects with this approach has led to stereotactic radiosurgery being investigated as an alternative treatment strategy. Radiosurgery is likely to offer effective local control while preserving WBRT for use as a salvatory therapy for distant brain failures. We report our initial experience using a linac-based frameless stereotactic radiosurgery (SRS) system. METHODS: We retrospectively analyzed outcomes, patterns of failure and the image-guided setup accuracy of the first 15 consecutive cases treated at Brigham and Women’s Hospital using image-guided (ExcacTrac by Brainlab) linear accelerator-based radiotherapy with a relocatable stereotactic frame and aquaplast mask (BrainLAB Mask System). The target volume was the resection cavity without a margin, excluding the surgical track. Median number of brain metastasis per patient was 1 (range 1–3). Median planning target volume was 3.3 cm³ (range 0.53–10.8 cm³). Median prescribed dose was 18 Gy with normalization ranging from 69 to 81%. Ninety-nine percent of the PTV was covered by the prescribed dose in all cases. Mean conformity index was 1.62 (range 1.41–1.92). RESULTS: At a median follow-up of 8.2 months (interquartile range 4.2–12.1), local control was achieved in 13 of 14 cases. True local recurrence occurred in 1 case. No marginal failures occurred. Distant brain failure occurred in 5 of 14 cases. Median time to any failure was 7.5 months. salvage therapy was administered in 15 patients (3 received WBRT, 1 received further radiosurgery, and 1 received systemic therapy only). No grade 3 or higher toxicity was recorded. Factors associated with lack of CNS failure (local or distant) included a single brain metastasis and long interval between initial cancer diagnosis and the development of brain metastasis. The frameless image-guided radiosurgery was delivered with submillimeter accuracy. The mean residual setup error was 0.45 mm (SD = 0.19 mm) and the mean intrafraction motion was 0.37 mm (SD = 0.31 mm). CONCLUSIONS: Image-guided frameless stereotactic radiosurgery to the postoperative resection cavity for brain metastasis is a safe and accurate technique that offers durable local control and postpones the use of WBRT in selected patients. This technique should be tested in larger prospective studies.
O.22. TREATMENT OF BRAIN METASTASES FROM NON–SMALL CELL LUNG CANCER WITH WHOLE-BRAIN RADIOTHERAPY (WBRT) IN COMBINATION WITH GEFITINIB (GFT) OR TEMOZOLOMIDE (TMZ): A RANDOMIZED MULTICENTER PHASE II TRIAL OF THE SWISS GROUP OF CLINICAL CANCER RESEARCH (SAKK #70/03)

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BACKGROUND: Patients with BM rarely survive >6 months and are commonly excluded from clinical trials. We aimed at improving outcomes by exploring 2 combined modality regimens with at the time novel agents for which single-agent activity had been shown. METHODS: NSCLC patients with multiple BM were randomized to WBRT (10 x 3 Gy) and GFT (250 mg p.o. daily) or TMZ 75 mg/m2 p.o. daily starting on Day 1 of RT and to be continued until PD. Primary endpoint was overall survival, a Simon’s optimal 2-stage design was based on assumptions for the 3-month survival rate. Cognitive functioning and quality of life were also evaluated. RESULTS: Fifty-nine patients (36 M, 23 F; 9 after prior chemo) were included. Median age was 61 years (range 46–82). WHO PS 0 was in 18 patients, 1 in 31 patients, and 2 in 10 patients. All but 1 patients had extracranial disease; 33 of 43 (TMZ) and 15 of 16 (GFT) had adenocarcinoma. A pre-specified 3-mo survival rate threshold (66%) was not reached, causes of death were not GFT related. Main causes of death were PD in the CNS 24%, systemic 41%, both 8%, and toxicity 10% [intestinal perforation (2 patients)]. Three patients (3%) died of toxicity. Median time to neurol. progr.: 8.0 months (95% CI 2.2–18 mo; Grade 3–4 toxicity: lymphopenia 5 patients (12%), fatigue 8 patients (19%), 2 patients (13%). Survival data for TMZ /GFT arms: 3-month survival rate: 58.1% (95% CI 42.1–73%) /62.5% (95% CI 35–85%); median OS: 4.9 months (95% CI 2.5–5.6) /6.3 months (95% CI 2.2–14.6); median PFS: 1.8 months (95% CI 1.3–1.8) /1.8 months (95% CI 1.1–3.9); median time to neurol. progr.: 9.0 months (95% CI 2.2–X) /4.8 months (95% CI 3.9–10.5). In a model to predict survival time including the variables’ age, PS, number of BM, global QL, total MMSE score, and subjective cognitive functioning, none of the variables accounted for a significant improvement in survival time. CONCLUSIONS: The combinations of WBRT with GFT or TMZ were feasible. However, in this unselected patient population, survival remains poor and a high rate of complication was observed. Four patients died as a result of high-dose corticosteroids. Preliminary evaluation of cognitive functioning and QL failed to show significant improvement. Indications and patient selection for palliative treatment should be revisited and careful monitoring and supportive care is required. Research and progress for this frequent clinical situation is urgently needed.

O.23. FREQUENCY, PATTERNS OF CARE, AND OUTCOME OF NEOPLASTIC METASTASIS (NM) FROM SOLID TUMORS IN THE REGIONE PIEMONTE, ITALY: A PROSPECTIVE SURVEY FROM A CANCER NETWORK

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BACKGROUND: Neoplastic metastasis (NM) is a devastating neurologic complication of cancer whose frequency and patterns of care are not well known. We investigated in a prospective survey, the frequency, patterns of care, and outcome of NM from solid tumors in a Community Hospital-based regional cancer network. METHODS: Clinical forms to collect data and clinical histories, signs, neurologic symptoms/scores, radiologic patterns, CSF cytology, treatment options, and outcome were sent to 29 neurologic and 42 medical oncology Services of the Regione Piemonte (Italy). Data on 59 patients (36 M, 23 F; 9 after prior chemo) were included. Median age was 61 years (range 46–82). WHO PS 0 was in 18 patients, 1 in 31 patients, and 2 in 10 patients. All but 1 patients had extracranial disease; 33 of 43 (TMZ) and 15 of 16 (GFT) had adenocarcinoma. A pre-specified 3-mo survival rate threshold (66%) was not reached, causes of death were not GFT related. Main causes of death were PD in the CNS 24%, systemic 41%, both 8%, and toxicity 10% [intestinal perforation (2 patients)]. Three patients (3%) died of toxicity. Median time to neurol. progr.: 8.0 months (95% CI 2.2–18 mo; Grade 3–4 toxicity: lymphopenia 5 patients (12%), fatigue 8 patients (19%), 2 patients (13%). Survival data for TMZ /GFT arms: 3-month survival rate: 58.1% (95% CI 42.1–73%) /62.5% (95% CI 35–85%); median OS: 4.9 months (95% CI 2.5–5.6) /6.3 months (95% CI 2.2–14.6); median PFS: 1.8 months (95% CI 1.3–1.8) /1.8 months (95% CI 1.1–3.9); median time to neurol. progr.: 9.0 months (95% CI 2.2–X) /4.8 months (95% CI 3.9–10.5). In a model to predict survival time including the variables’ age, PS, number of BM, global QL, total MMSE score, and subjective cognitive functioning, none of the variables accounted for a significant improvement in survival time. CONCLUSIONS: The combinations of WBRT with GFT or TMZ were feasible. However, in this unselected patient population, survival remains poor and a high rate of complication was observed. Four patients died as a result of high-dose corticosteroids. Preliminary evaluation of cognitive functioning and QL failed to show significant improvement. Indications and patient selection for palliative treatment should be revisited and careful monitoring and supportive care is required. Research and progress for this frequent clinical situation is urgently needed.

O.24. STEM CELL TRANSPLANTATION FOR CNS RECURRENTENCE OF SYSTEMIC NHL: AN INTERNATIONAL PRIMARY CNS LYMPHOMA GROUP (IPCG) PROJECT

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BACKGROUND: Prognosis is poor in patients with relapsed lymphoma with central nervous system (CNS) localization. In chemosensitive-relapsed systemic lymphoma without CNS localization, autologous stem cell transplantation (ASCT) is the treatment of choice and is able to increase the long-term survival rate, especially when combined with rituximab. Small retrospective series of ASCT-treated patients have shown that this treatment is feasible in selected cases with CNS recurrence, but no prospective data are available. Given the rarity of the disease, an international collaboration within the IPCG was formed to obtain data on patients from a variety of countries. METHODS: From affiliated and interested centers performing ASCT, all patients with a CNS localization of systemic lymphoma at first recurrence or progression potentially eligible for ASCT were selected from local databases. Anonymized data were collected on primary disease, recurrence or progression, treatment of recurrence or progression, result and toxicity of this treatment, and survival. RESULTS: From 6 centers in 5 countries, 72 patients were identified. Initial treatment varied but contained intrathecal treatment or prophylaxis in 13 patients, and systemic rituximab in 32. Initial symptoms of the relapse were of CNS disease in 50 patients, of systemic disease in 7, and of both in 14. In path the CNS, ASCT was performed in 37 patients, only 36% had a leptomeningeal localization with or without a parenchymal lesion. Patients initially treated with rituximab had an increased risk of CNS parenchymal relapse: 74% compared with 44% in patients who were rituximab naïve (P = .014; χ² test). Of the 6 patients who received rituximab, only 93% of patients was treated with HD-MTX or HD-cytarabine containing regimens. Twenty-four patients were not eligible for transplantation because of age, prior transplantation, or unknown reasons. Of the remaining 48 patients, 17 (35%) received ASCT. Median survival from the time of CNS relapse in all patients was 8 months, and that in transplanted patients >49 months. Survival at 1 year after transplantation was 81%. CONCLUSIONS: Significantly more patients initially treated with rituximab had a CNS parenchymal lesion rather than leptomeningeal localization only. Only 35% of patients potentially eligible for transplantation was transplanted; those reaching transplantation had favorable survival following transplantation.

CELL BIOLOGY/IMMUNOTHERAPY

O.25. BONE MARROW-DERIVED CELLS INTERACT WITH GLIOMA CELLS DURING TUMOR DYNAMICS AND ANGIOGENESIS

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Hematopoietic progenitor cells (HPCs), but also mature blood cells, are increasingly investigated regarding their role for tumor angiogenesis, with
conflicting results for brain tumors. Moreover, their role for brain tumor invasion is not defined. We therefore aimed to investigate the kinetics of recruitment, the spatiotemporal interaction with tumor vessels and hematopoietic cells, and the migratory pattern of intravenously applied cells from the bone marrow of β-actin eGFP transgenic mice: (a) lineage depleted hematopoietic precursor cells (lineage negative = CD5−, CD11b−, CD19−, CD45R−, Ly-6G−, TER119−); (b) hematopoietic stem cells (lin−, Sca−1+); and (c) mature macrophages (lin+ + , CD115+). To achieve this aim, multiphoton laser scanning microscopy (MPLSM) in combination with a chronic cranial window was used to image both red-fluorescent U87 glioma cells and eGFP-expressing cell populations (a−c) within the glioma micromilieu. Blood vessels were highlighted by yellow fluorescence.

After i.v. injection, all three cell populations showed a specific homing into the glioma, with a characteristic kinetic for each of them, ranging from immediate (maximum day 1) to late (maximum day 7) homing. The bone marrow-derived cell lines displayed typical morphological features after extravasation into the glioma. Incorporation into glioma vessels happened only occasionally and in a pericyte-like position; however, bone marrow-derived cells showed the ability to proliferate over time and become part of the vascular wall. Interestingly, a very small subset of U87 glioma cells migrated throughout the tumor. Tumor cell migration exclusively occurred in close vicinity to bone marrow-derived cells, suggesting a potential role for tumor invasion. In conclusion, our study provides the first in vivo investigation of dynamic interactions of brain tumor and hematopoietic cells. We could identify specific actions that support a role of hematopoietic cells in glioma progression.

O.26. NOTCH PATHWAY BLOCKADE AFFECTS THE MIGRATORY AND DIFFERENTIATING CAPACITY OF BRAIN TUMOR INITIATING CELLS

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BACKGROUND: The high-grade glioma, glioblastoma multiforme (GBM) is the most common and aggressive primary brain tumor in adults, and represents a significant therapeutic challenge. The majority of GBM’s is often difficult to operate, because of their location and infiltrative growth pattern, and nonsurgical treatments (chemo- and radiation therapy) are often ineffective. As such, relapse and/or mortality is almost certain and new treatment modalities are urgently needed. Brain tumor initiating cells (bTICs) are a population of neural stem cell (NSC)-like cancer cells reported in GBM. bTICs are increasingly being assigned a central role in brain tumor initiation, progression, treatment resistance, and relapse and are suggested as a novel target in glioma therapy. The Notch signaling pathway is important in maintaining an undifferentiated pool of normal NSC and in determination of cell fate. Components of the Notch pathway are often found aberrantly expressed in GBM and might be crucial to maintaining a niche supportive of tumor initiation. When neurosphere cells were induced to differentiate during DAPT inhibition of cell migration, in a modified Boyden chamber, upon Notch blockage, the differentiated Notch pathway was demonstrated to play a role in the in vitro tumorigenic potential of the GBM neurosphere line. A. Bohne-Kjær, P. Sakrørrassen, V. Bjerkgård, J. I. Heggdal, P. Ender, K. J. Tronstad, and W. Van Furfth;

O.27. NG2 PROMOTES RESISTANCE TO IONIZING RADIATION BY ELEVATED PEROXIREDOXIN-1 AND DNA DAMAGE RESPONSE IN Glioblastoma MULTIFORME

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Glioblastoma multiforme (GBMs) are lethal cancers that respond poorly to radiotherapy and the mechanisms may involve stem/progenitor cells. Several studies proclaimed that brain tumors enriched in CSCs were preferentially resistant to ionizing radiation and chemotherapy as a result of altered checkpoint and DNA repair pathways compared with conventional tumors. Others have claimed that these cells are associated with increased reactive oxygen species and that this is an additional mechanism for radiation resistance. Since the glial progenitor marker NG2 has been shown to regulate tumor response to chemotherapy, we examined whether it also affected response to radiotherapy. Quantification of NG2 expression in 96 patient GBM biopsies revealed that high expressers had shorter survival outcomes than low expressers, P = .02. Two-dimensional (2D) proteomics of 11 of these biopsies showed that peroxiredoxin-1 (PRDX-1) was upregulated in the shortest surviving patients, and was associated with reduced oxidative damage. Furthermore, NG2 expressing GBMs were highly resistant to ionizing radiation (IR) in vitro and in vivo and increased PRDX-1 levels in a dose-dependent manner, shRNA-mediated NG2 knockdown inhibited the tumor cells to IR and attenuated dose-dependent induction of PRDX-1. Moreover, NG2 expressing cells rapidly induced DNA damage response signaling as indicated by phosphorylation of H2AX, ATM, and Chk2 proteins compared with NG2-negative cells. PRDX-1 knockdown transiently slowed tumor growth rates in vitro and partially sensitized the tumors to ionizing radiation in vivo. These data demonstrate a novel role for NG2 in mediating radioreistance in human GBMs by interaction with PRDX-1 and DNA damage response machinery.

O.28. CD44 LOSS OF FUNCTION IMPEDES GLIOMA PROGRESSION IN A SPONTANEOUS MURINE MODEL

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CD44 is a transmembrane receptor for hyaluronan that coordinates intracellular signaling and cytoskeleton rearrangements in response to cues from the extracellular matrix. As brain tumors develop in a hyaluronan-rich environment, overexpression of CD44 can lead to the enhancement of proliferation, migration, and survival facilitated by CD44. We have developed a murine model of gliomas that is uniquely suited for the evaluation of CD44 loss of function studies. Malignant glioma cells were induced in mice by transfecting plasmids encoding SV40LG and NRasG12V into the lateral ventricle of wild-type (CD44+/+) and knock-out (CD44−/−) mice. Tumor progression was monitored weekly using bioluminescent imaging and directly correlated with tumor burden. Grade 3−4 gliomas developed in CD44+/+ mice within 1 month of oncogene delivery. These tumors advanced rapidly as assessed by steadily increasing bioluminescent imaging and a median survival of 39 days. Two-color immunohistochemistry (IHC) was developed against CD44 and SV40LG to detect CD44 expression within the bulk tumor and the infiltrative glioma cells. IHC studies have shown remarkably similar phenotypes of CD44 overexpression in both mouse and human tumor specimens. In addition, CD44 positive tumor cells can be found infiltrating into the perivascular space in the normal brain of tumor bearing mice. In contrast to CD44+/+ rapid tumor growth, CD44−/− tumors have a significant delay in progression (median survival = 50 days). Importantly, a subset of tumors in CD44−/− mice spontaneously regressed and a hallmark of this was increased PRDX-1. Moreover, CD44 loss of function was rescued by expressing murine CD44 cDNA in cis to the NrasG12V plasmid. The significant extension of survival in CD44−/− mice is abolished when CD44 expression is rescued exclusively in the tumor cells. These glioma cells require CD44 to maintain a niche supportive of tumor cell self-renewal and survival. Ongoing studies will look at CD44 modulation of multidrug transporter activity and sensitivity to chemotherapeutic agents because of loss of function of CD44.
Glioblastoma multiforme (GBM) is a lethal subgroup of intracranial tumors with a median survival of 14.6 months, despite multimodal treatment. We have previously shown that several treatment resistant tumors aberrantly express the neural progenitor marker NG2. We therefore aimed to target NG2 in GBMs using the 9.2.27 mAb and adoptively transferred autologous natural killer (NK) cells and to determine if this combination anti-tumor effect. The NK cells and mAb were infused intratumourally by convection-enhanced delivery (CED) in rat brains transplanted with human GBM xenografts, as well as syngeneic rat gliosarcoma. Magnetic resonance imaging was used to longitudinally monitor the tumor growth characteristics. Combined NK+ mAb targeting resulted in significantly longer survival times compared with the vehicle, and monotherapy controls (U251-NG2: log-rank test, \( P = .0081 \); U87: log-rank test, \( P = .0003 \)). Histological analyses revealed strong presence of MPO, granzyme, and IFNγ-expressing granulocytic cells in focal areas of strong necrosis/apoptosis in the NK+ mAb- and mAb-treated groups. Moreover, double-labeling revealed the greatest numbers of M1-type macrophages that were ED1+, CD8+ positive cells that were abundant and remained at the tumor brain boundary. M1RI revealed tumor growth arrest in many NK+ mAb-treated animals, whereas mAb-treated tumors displayed reduced contrast enhancement and necrosis. In conclusion, combined 9.2.27 mAb and NK cell therapy strongly affected tumor growth and vascular parameters and prolonged survival. Thus, adoptive cell therapy with NK cells may be an aminable therapy for treatment-resistant GBMs.

**O.30. PHASE III ANTI-EGF-RECEPTOR ANTIBODY (OSAG-101) FOR NEWLY DIAGNOSED GLIOBLASTOMA: SAFETY AND CURRENT STATUS**

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The epidermal growth factor receptor, EGFR-R, is considered a highly relevant therapeutic target for glioblastoma resulting in a wide spectrum of approaches directed against the intercellular signaling pathway, the ligand binding capacity, and the intracellular immunoreceptor tyrosine-based activation motifs (ITAM) splice variant. Because of promising preclinical and early clinical findings, the evaluation of the therapeutic effect of a monoclonal antibody against the EGF-R (nimotuzumab) which has a lower affinity than cetuximab, thus binding more specifically to highly expressing cells was undertaken in a phase III design. Nimotuzumab (OSAG-101) was tested in an open-label, randomized, multicenter phase III trial in patients with newly diagnosed glioblastoma. OSAG-101 is administered by i.v. infusion (weekly infusion of 400 mg) in addition to the current standard therapy with concomitant radiochemotherapy using temozolomide followed by biweekly infusions of 400 mg temozolomide thereafter. Nimotuzumab administration in this trial was to continue until progression. Patients with histologically confirmed glioblastoma were included without specification of resection status. Patients under the age of 18 and over 70 years were excluded. Primary endpoint was time to progression as determined by centralized review of standardized MRI and a prespecified evaluation protocol. OSAG-101 was chosen as a secondary endpoint with quality of life and safety as additional parameters. Between August 2008 and March 2010, 145 patients were enrolled in 10 sites with 165 subjects. All except one patient were GBM on central histopathological review. Just <50% of the patients had a gross total resection with no residual contrast enhancement whereas the larger group had partial resections with residual contrast enhancement, including patients with biopsy only. The observed adverse reaction pattern was the same in both study arms and both strata and reflected the toxicity of the disease and its standard treatment. Specifically, no rash, conjunctivitis, or mucositis as known for anti-EGF-R reagents were reported. We conclude from the trial so far that the intravenous administration of OSAG-101 for newly diagnosed glioblastoma is safe and free of additional toxicity to the standard radiochemotherapy regimen. Seventy-five patients have reached their primary endpoint at this point and an interim analysis is currently conducted to provide first indications for efficacy. Accrual is expected to be complete by the end of May 2010.

**MENINGEOMA AND PEDIATRIC BRAIN TUMORS**

**O.31. THE EFFECT OF EDEMA ON HEALTH-RELATED QUALITY OF LIFE IN WHO GRADE I MENINGIOMA PATIENTS**

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BACKGROUND: Studies on the associations between pre- and postoperative cerebral edema and quality of life in WHO grade I meningioma patients are virtually lacking. In patients with other types of brain tumors, associations between cerebral edema and clinical symptoms have been shown. Edema may contribute to the deficits in neurological and cognitive functioning, and consequently to aspects of patients’ quality of life. AIM OF THE STUDY: To determine the effects of pre- and postoperative cerebral edema on health-related quality of life in WHO grade I meningioma patients. METHODS: Two hundred fifty WHO grade I meningioma patients were individually matched to 25 healthy controls for age, sex, and educational level. We determined functional status and HRQOL at least 1 yr postoperatively. Furthermore, we determined the volume of cerebral edema on pre- and postoperative (3 months) MRI scans. The contribution of cerebral edema on HRQOL was investigated by correlational analysis. RESULTS: No significant differences were found in HRQOL between meningioma patients and healthy controls. However, 76% of patients reported a high level of fatigue; 32% reported to be depressed. Both pre- and postoperative tumor-related edema volume were found to be a significant predictor of the patients’ physical and social functioning, and bodily pain. CONCLUSIONS: The present study suggests an important role for cerebral edema in HRQOL in meningioma patients. Meningioma patients with a significant amount of cerebral edema seem to be at risk for developing psychological problems and should therefore be screened neuropsychologically. Further research should be focused on the effect of treatment of cerebral edema on the one hand, and the impact of neuropsychological interventions on the other hand on HRQOL in meningioma patients with edema.

**O.32. HYPOFRACTIONATED STEREOTACTIC RADIOTHERAPY OF THE OPTIC NERVE SHEATH MENINGIOMAS: AN EFFECTIVE OPTION**

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OBJECTIVE: The management of primary Optic Nerve Sheath Meningiomas (ONSMs) is still controversial. Surgery easily leads to a complete blindness of the affected eye. On the other hand, the role of conventional radiotherapy remains uncertain and literature lacks of data to confirm its usefulness. The aim of this study was to evaluate the level of effectiveness and safety of CyberKnife® (Accuray Incorporated) stereotactic radiosurgery as first-choice treatment for optic nerve sheath meningiomas. METHODS: In the period between May 2004 and June 2008, we treated 21 patients affected by ONSMs, with the frameless CyberKnife system. The mean tumor volume ranged from 36 to 73 mm3. All the patients gave their informed consent. The prescribed dose was 25 Gy prescribed to the 70%–85% isodose line. All patients were treated with a Stereotactic Radiotherapy treatment; particularly, they underwent a 25-Gy treatment in 5 fractions. Before the treatment, 3 patients had a conserved visual function whereas 11 presented a deficit of the sight or of the visual field. Seven patients were blind. Patients were evaluated both for the tumor growth control and the visual function. RESULTS: The mean follow-up period was 21 months (range 7–56 months). All patients welltolerated the procedures. Only 1 patient developed a mild optic neuropathy (remitted after a systemic steroid therapy). No others’ acute or late radiation induced toxicities were observed. The median of tumor volume was 2.8 cc (range 0.3–23 cc). No patients showed a progression disease at MRI
controls. Two patients (9%) had a partial response. No patients had a worsening of the visual function. If we considered only the patients with a partial deficit of the sight or visual field, 60% showed an improvement. CONCLUSIONS: ONSD frameless stereotactic radiotherapy as found to be safe and effective. Tumor growth control was complete and visual function was maintained or improved. If the long-term follow-up will sustain the preliminary results, stereotactic radiotherapy could become the new first-choice treatment.

O.33. SURVIVAL AND FUNCTIONAL OUTCOME OF MENINGIOMA PATIENTS: LONG-TERM DISABILITY AND POOR SURVIVAL
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INTRODUCTION: The 5-yr control rates of WHO grade I meningioma as reported in the literature is ~90% after complete resection and ~65% after a non-radical resection. The role of adjuvant radiotherapy (RT) is debated. Although survival is generally described as favorable, we found earlier that cognition and quality of life are impaired in many long-term meningioma survivors. OBJECTIVE: In the retrospective series of a large neurosurgical series we report long-term results in terms of survival, tumor recurrence, and functional outcome. METHODS: Analysis of all 212 patients after a neurosurgical resection for WHO grade I benign intracranial meningioma between 1985 and 2003: 159 females (70%) and 63 males (30%) with an average age of 53 (±13.9) yr at first diagnosis. Thirty-five (16.5%) patients received RT. Mean follow-up was 11.4 (±5.1) years. Long-term functional outcome was assessed by a mailed questionnaire to the general practitioner. Statistical analysis including Cox-multivariate analysis was performed with SPSS. The age- and gender-specific survival was calculated by applying Dutch life-table statistics to each individual patient for the individual duration of follow-up. RESULTS: The overall survival at 5, 10, 15, and 20 years was 95%, 81%, 63%, and 54%, respectively. This is substantially lower than the expected age- and sex-specific survival for this specific group, calculated at 94%, 86%, 79%, and 66%, respectively. In a multivariate analysis, survival was better with a lower Simpson grade (P = .018) and a lower age at diagnosis (P < .0001). Tumor progression rates at 5, 10, and 15 yr were 17%, 26%, and 32%. Lower Simpson grade (P = .002), Karnofsky performance score > 70 before surgery (P = .05), and a lower age at diagnosis (P = .033) were associated with a lower recurrence rate. Eight patients (4%) had adjuvant RT; 27 patients (13%) received salvage RT for recurrent disease. RT was associated with a worse survival (P = .08) and a higher recurrence rate (P < .0001). After first surgery, 27 (13%) patients did not show any remission and 46 (22%) had more symptoms. CONCLUSION: Despite the benign histology of meningiomas, the long-term survival is severely challenged by the tumor and its complications; one-third of patients has stable or progressive symptoms. The role of radiotherapy remains unclear, since radiotherapy was mostly reserved for salvage treatment of recurrent disease.

O.34. SECOND-LOOK SURGERY (SLS) FOR EPENDYMOMA: THE ITALIAN EXPERIENCE
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INTRODUCTION: Complete resection of ependymoma is associated with better PFS/OS; smaller residues are even associated with better prognosis than “bulky” residues. According to experienced neurosurgeons, a truly complete excision of an infratentorial ependymoma is not feasible without serious risks whenever tumor arises from the floor of the fourth ventricle. SLS on smaller tumors can be associated with less dangerous anesthesiologic conditions and reach complete tumor removal. In this view, there is a possible, still uncertain, role for neo-adjuvant chemotherapy in preparing further surgical approaches. METHODS: From 1994 up to now, we have adopted two subsequent protocol for intracranial ependymomas: in both a phase of adjuvant chemotherapy was prescribed for children with surgical residues, before radiotherapy, in view of possible SLS before it. In the first protocol, that accrued a total of 63 children, 9 were submitted to more than one surgical act: 4 after the 1st excision and 5 after surgery and chemotherapy: 3/4 plus 3/5 were rendered CR without additional sequelae, and their prognosis both for PFS and for freedom from local relapse was comparable to that of children operated once. In the subsequent protocol the efforts toward complete resection were improved. RESULTS: Of 95 patients accrued from 2001 to 2009, 29 had measurable disease after 1st surgery and/or adjuvant chemotherapy. Twenty-two were re-operated: 5 after 1st surgery, 15 after chemotherapy, and 2 soon after radiotherapy; 2 children had 3 and 1 had 4 excisions. Eleven of 22 patients obtained CR: one had a neurologic worsening. We compared the outcome of the 38 patients CR after one surgic- al act with those 11 obtaining CR after more acts: both groups had 3- and 5-year PFS of 66% and 3-year freedom from local relapse was 82% and 87%, respectively. Discussion: SLS demonstrated feasible without major morbidity and results improved during the years. Local tumor control because of SLS was comparable in patients with one and multiple resection.

O.35. THIRTY-FIVE YEARS OF SURGICALLY TREATED PEDIATRIC MENINGIOMAS IN THE NETHERLANDS: A DESCRIPTIVE EPIDEMIOLOGICAL CASE STUDY
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OBJECTIVE: To review and describe the epidemiology and the clinical, radiological, pathological, and management profile of all pediatric meningiomas surgically treated during the last 35 years in the Netherlands. MATERIAL AND METHODS: All pediatric patients (<18 yr of age) with the diagnosis meningiomas, treated at one of the neurosurgical centers in the Netherlands during the last 35 years, were identified in the PALGA database, the nationwide network, and registry of histo- and cytopathology. Data were retrieved from clinical records, radiological findings, operative reports, and pathological examinations. RESULTS: In total, 115 registries of meningioma histology in pediatric patients were identified in the PALGA database. Forty-six cases were excluded because either the histological diagnosis was a revision and confirmation of the original histology, or the original histological diagnosis was changed after revision. Thus, 69 patients (37 males, 32 females) with 115 meningiomas were included, making this the largest study of its kind. Clinical presentation: the most common symptom was raised intracranial pressure (30%). Mean age at diagnosis was 11.7 yr (0.3–18.8). Location: most frequently on the convexity (22%). Histology: 11 patients (16%) had neurofibromatous type 2 and 4 patients received prior radiotherapy. Histology: 42 patients (61%) had a WHO grade I, with meningothelialomatous meningioma as most common histological subtype. Five patients (7%) had a WHO grade III tumor. Surgery: macroscopic total resection was accomplished in 31 patients (42%) and subtotal in 10 patients (30%). Simple decompression was used in 5 patients (7%). Resection grade was missing in 14 patients (21%). Additional treatment: 15 patients (22%) received radiotherapy postoperatively. Follow-up: mean follow-up was 4.9 yr (0–27.8). A total of 22 radiological confirmed recurrences were diagnosed in 15 patients (29%) during a period of 3.9 yr (0.1–26.3). Eleven tumors recurred after macroscopic total resection. Nine patients with a recurrent tumor were first diagnosed with a WHO I (69%), none with a WHO III tumor. Six patients (9%) died as a result of their meningioma. CONCLUSION: Pediatric meningiomas are extremely rare. This is the first single-country study and one of the largest childhood series on this tumor. The presentation and biological behavior is different compared with meningiomas in adults. A high recurrence rate is observed and outcome tends to be worse.

O.36. DOSE CONSTRAINT MODEL TO PREDICT NEUROCOGNITIVE OUTCOMES IN YOUNG PATIENTS WITH LOW-GRADE BRAIN TUMORS TREATED WITH STEREOTACTIC CONFORMAL RADIO THERAPY
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BACKGROUND: To analyze the effect of radiotherapy (RT) dose levels on various brain structures as a model to preserve neurocognition in young patients with low-grade brain tumors treated prospectively with stereotactic conformal radiation therapy (SCRT). MATERIALS AND METHODS: Thirty-five patients (median age 13 yr) with low-grade and benign residual/progressive brain tumors (craniopharyngioma, cerebellar astrocytoma, charismatic hypothalamic glioma, other low-grade glioma) were...
treated with SCRT to a dose of 54 Gy/30 Fr/6 weeks with 2- and 3-year follow-up were analyzed. Prospective neuropsychological assessment were done at baseline pre-RT and at subsequent follow-up with an age-appropriate neuropsychological battery of tests. The change in intelligent quotient (IQ) scores was correlated with various factors and dose volumes to normal brain structures using logistic regression analysis. RESULTS: One-third of patients had >10% drop in FSQI over baseline. Comparison of dosimetric data in patients showing a significant drop (>10%) in IQ with patients with maintained IQ revealed that patients receiving >42.5 Gy (80% of the prescribed dose) to >13% of volume (P = .048) and >27 Gy (50% of the prescribed dose) to >50% of the volume of left temporal lobe were the ones to show significant drop in FSQI (P = .06). Doses to the hippocampus are being analyzed and show a positive trend toward its association and a decline in cognition.

CONCLUSION: Our detailed dosimetric data show a possible dose constraint model for high-precision RT planning to prevent a decline in neurocognition. FSIQ (volume of left temporal lobe were the ones to show significant drop in

MOLECULAR MARKERS II

O.37. CI-PERINOMS: CHEMOTHERAPY-INDUCED PERIPHERAL NEUROPATHY OUTCOMES STUDIES

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Chemotherapy-induced peripheral neuropathy (CIPN) is a major, frequent, and potentially dose-limiting adverse event of a wide variety of chemotherapeutic agents. Despite its relevance, no formally validated instruments to assess the occurrence and the severity of CIPN have been described so far. The aims of CI-PERINOMS are (i) to evaluate through a multi-center, international collaboration among experienced neurologists and oncologists the best method(s) available to assess and monitor CIPN, (ii) to determine the validity and reproducibility of the proposed outcome measures, and (iii) to produce a CIPN-specific disability sum score based on the selection of relevant questions from a large database. The study started in January 2009 and it is planned that patients’ enrollment will be completed by December 2010 or at the recruitment of 300 patients. So far 20 European/US centers (*) received EC approval and 151 patients have been enrolled at 16 centers. According the study protocol, inter- and intraobserver comparison and test–retest studies are to be performed by two investigators in each participating center on patients with a stable CIPN. The scales/instruments used in the study are: TNSc = Total Neurology Score, classical version; VAS = visual analogue pain scale; PI-NRS = 11-point pain intensity numerical scale; C-ODDS = calibrated-overall disability sum score; NCI-CTC = National Cancer Institute-Common Toxicity Criteria, version 3; QLQ-CIPN20 EORTC = quality of life questionnaire for CIPN; QLQ-C30 = EORTC 30-item questionnaire for cancer patients; QoL-PS = quality of life personal score; and mNSS = modified INCAT sensory sum score. A small battery of nerve conduction studies is conducted to each patient, in order to compare the neurophysiologic results with those obtained with clinical methods. We are convinced that the results of this study will improve the knowledge on CIPN and will be useful in designing future studies to prevent or ameliorate CIPN.


O.38. GLUT1/SLC2A1 IS CRUCIAL FOR DEVELOPMENT OF BRAIN MICROVASCULARITY WITH BLOOD–BRAIN BARRIER (BBB) PROPERTIES IN VIVO: POTENTIAL CLINICAL IMPLICATIONS

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Glucose transporter 1 (Glut1) is expressed at high levels in the capillary endothelial cells of barrier such as the blood-brain barrier (BBB). In normal brain of human, rodent and zebrafish Glut1 is selectively present in the cerebral capillary endothelium. The BBB is composed of tightly linked cerebral endothelial cells sealed by tight junctions (TJ) and adherens junction (AJs). Bedside Glut1 and the TJ/AJ proteins are concomitantly downregulated in human high-grade gliomas and some other situations in which BBB breakdown has taken place, we hypothesized that this molecule may play a significant role in the development of cerebral capillaries with BBB properties. The homologue Glut1 amino sequence in zebrafish is highly similar to that of humans and, therefore, the zebrafish is eligible as a model organism for the investigation of the human Glut1 gene. In our zebrafish model of Glut1 knockdown, the development of the cerebral microvasculature appeared to be interrupted with reduced expression of the TJ/AJ proteins and induced vasogenic brain edema. The data provide the first functional assessment of the role of Glut1 in the development of the cerebral capillary endothelium in vivo and suggest a crucial role of this molecule in the development of the cerebral microvasculature and formation of the BBB. Therefore, modulation of Glut1 expression and function may well provide a new treatment option in the treatment of BBB disruption in devastating brain disorders.

O.39. TIMP-1 AND THE TIMP-1 INTERACTING CELL SURFACE PROTEIN CD63 IN CULTURED ASTROCYTOMA DERIVED STEM CELL MARKERS

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In previous studies, we have shown that the immunohistochemical expression of TIMP-1 (tissue inhibitor of metalloproteinases-1) and CD63 increases with tumor grade in astrocytomas grade II–IV. Moreover, we demonstrated that a high TIMP-1 protein expression in glioblastomas was associated with a shorter overall patient survival. Recent studies have suggested that TIMP-1 can prevent chemo-induced apoptosis and, in a study, using human brain epithelial cells (MCF10A), it was demonstrated that the interaction of TIMP-1 and CD63 is necessary for the TIMP-1 anti-apoptotic pathway. The aim of the present study was to investigate the expression of TIMP-1 and CD63 in cultured organotypic multicellular spheroids (OMS) and cell line spheroids (CLS) derived from astrocytomas in order to assess spheroid models for future studies involving TIMP-1, CD63, and chemoresistance. By investigating the spheroids immunohistochemically, we wanted to elucidate whether TIMP-1 and CD63 are co-expressed within the spheroids and whether they are expressed by tumor stem-like cells, since these cells are known to be more resistant to chemotherapeutic treatment. In the present study, OMS from 9 astrocytomas and CLS from 3 commercial astrocytoma cell lines were included as well as the glioblastoma tumor stem cell line SJ-56 made in our laboratory. In general, high levels of CD63 protein were detected in all the original tumors, whereas TIMP-1 was moderately expressed. TIMP-1 and CD63 expression in OMS was similar to the expression in the original tumors. TIMP-1 was expressed at low-to-moderate levels in CLS, whereas CD63 was expressed by all tumor cells in all spheroids. TIMP-1/CD63 double immunofluorescence staining was performed on selected OMS and CLS showing tumor cells expressing both proteins. Furthermore, double staining was performed with TIMP-1 and the stem cell markers CD133, nestin, and Sox2, demonstrating that a population of the tumor stem-like cells expressed TIMP-1. In conclusion, this study shows that spheroid models can be used in future studies investigating the role of TIMP-1 and CD63 in chemo-induced apoptosis. Furthermore, these results indicate that a fraction of the tumor stem-like cells could be protected by TIMP-1–CD63 interaction.

O.40. MYELODYSPLASIA IN PRIMARY BRAIN TUMOR PATIENTS TREATED WITH ALKYLATING AGENTS

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BACKGROUND: Treatment-related myelodysplastic syndrome (t-MDS) and acute myelogenous leukaemia (t-AML) represent rare secondary events in patients with primary tumors of the nervous system. The emergence of temozolomide as an effective alkylating agent with little acute toxicity or side effects has led to its protracted use in patients with primary tumors of the nervous system. The emergence of t-MDS and t-AML represent rare secondary events in patients with primary tumors of the nervous system. The emergence of t-MDS and t-AML represent rare secondary events in patients with primary tumors of the nervous system. The emergence of t-MDS and t-AML represent rare secondary events in patients with primary tumors of the nervous system. The emergence of t-MDS and t-AML represent rare secondary events in patients with primary tumors of the nervous system.

In a study, using human brain epithelial cells (MCF10A), it was demonstrated that the interaction of TIMP-1 and CD63 is necessary for the TIMP-1 anti-apoptotic pathway. The aim of the present study was to investigate the expression of TIMP-1 and CD63 in cultured organotypic multicellular spheroids (OMS) and cell line spheroids (CLS) derived from astrocytomas in order to assess spheroid models for future studies involving TIMP-1, CD63, and chemoresistance. By investigating the spheroids immunohistochemically, we wanted to elucidate whether TIMP-1 and CD63 are co-expressed within the spheroids and whether they are expressed by tumor stem-like cells, since these cells are known to be more resistant to chemotherapeutic treatment. In the present study, OMS from 9 astrocytomas and CLS from 3 commercial astrocytoma cell lines were included as well as the glioblastoma tumor stem cell line SJ-1 made in our laboratory. In general, high levels of CD63 protein were detected in all the original tumors, whereas TIMP-1 was moderately expressed. TIMP-1 and CD63 expression in OMS was similar to the expression in the original tumors. TIMP-1 was expressed at low-to-moderate levels in CLS, whereas CD63 was expressed by all tumor cells in all spheroids. TIMP-1/CD63 double immunofluorescence staining was performed on selected OMS and CLS showing tumor cells expressing both proteins. Furthermore, double staining was performed with TIMP-1 and the stem cell markers CD133, nestin, and Sox2, demonstrating that a population of the tumor stem-like cells expressed TIMP-1. In conclusion, this study shows that spheroid models can be used in future studies investigating the role of TIMP-1 and CD63 in chemo-induced apoptosis. Furthermore, these results indicate that a fraction of the tumor stem-like cells could be protected by TIMP-1–CD63 interaction.

Case reports and small case series of patients with t-MDS and t-AML during or after treatment with alkylating chemotherapy for a primary brain neoplasm were identified through a comprehensive search of the PubMed
database of the US National Library of Medicine. We recorded type of alkylat-
ing and other chemotherapy agents used, dose, concomitant or sequential irradiation, genetic predisposition, type of myogenous tumor, cytogenet-
ics, findings, latency between completion of chemotherapy and diagnosis of t-MDS/t-AML, treatment, and outcome. RESULTS: We identified 39 cases fulfilling eligibility criteria. There were 17 male and 16 female patients (gender not listed in 6) with a median age of 20 years [range 0.25−69 yr]. The most common primary tumor was anaplastic astrocytoma (9) followed by medulloblastoma, low-grade astrocytoma (6 each), glioblastoma (5), and choroid plexus papilloma (3). Twenty-eight patients developed t-MDS. Of those, 12 progressed to t-AML. In 11 patients, t-AML was the first hematolo-
gic diagnosis. Median interval between completion of chemotherapy and diagno-
sis of t-MDS/t-AML was 17 months [range 0−29 months]. Patients received lomustine, carmustine, nimustine, procarbazine, temozolomide, and treatment (exposure to ionizing radiation and mutagenic chemotherapeu-
tic agents). Studies regarding the individual leukemogenic potential of these therapies are lacking and their individual contribution and possible synergisms remain unsolved.

**O.41. CHEMOTHERAPY-INDUCED POLYNEUROPATHY SCORE (CIPS): A NEW TOOL IN THE DIAGNOSIS OF CHEMOTHERAPY-INDUCED POLYNEUROPATHY (CIPN)**

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INTRODUCTION: Chemotherapy-induced polyneuropathies (CIPN) are representing a therapy-limiting factor in the treatment of different oncolo-
gic diseases. Recognition and diagnosis of CIPN is impossible to prevent patients from neurotoxicity induced loss of neurological function. The total neuropathy score (TNS) is currently the most frequently used score to assess CIPN. However, evaluation of CIPN by means of the TNS is rather time-consuming, and needs to be done by neurological trained personnel. Therefore, practical application of the TNS for everyday clinical use is difficult. The purpose the study was to design a simple, prac-
ticable questionnaire (CIPS), which can easily be used in the clinical setting. METHODS: The CIPS was created from elements of the validated TNS and clinic-neurological experience. In this consecutive prospective study, 21 chemo-naïve patients with colorectal carcinoma and adjuvant oxaliplatin chemotherapy were included. All patients were treated and tested at the Oncology Department of the KI-Hospital in Vienna. Patients were examined with the TNS and the study questionnaire CIPS at baseline, at the 4th and at the 6th cycle of chemotherapy. RESULTS: Of 21 included patients, 4 patients were drop-outs. From 17 remaining study participants, 15 (85%) developed a CIPN and 9 (60%) study participants an acute 

**O.42. THE POTENTIAL ROLE OF VASCULAR ENDOTHELIAL GROWTH FACTOR IN RADIATION NECROSIS OF THE BRAIN, FROM THE PATHOLOGICAL CONSIDERATION OF HUMAN SURGICAL SPECIMEN**

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PURPOSE: With the advancement of high-dose radiation therapies for brain tumors, radiation necrosis has become a great problem. Here, we describe the potential role of vascular endothelial growth factor (VEGF) in radiation necrosis (RN) of the brain from a pathological and immunohistochemical point of view. MATERIALS AND METHODS: From June 2004 to July 2009, we treated 27 cases of symptomatic RN in the brain. These cases included different tumor histology, such as glioblastoma, metastatic brain tumor, and malignant meningioma, and were treated with different radiation modalities. Follow-up medical treatment included mainly oral steroids, anticoagulants, vitamin E, and others for at least 1-month duration. For 18 patients who were refractory to these medical treatments, we per-
formed surgical excision of the necrotic mass. The surgical specimens were analyzed histopathologically with hematoxylin and eosin (H&E) staining and anti-VEGF immunohistochemistry. RESULTS: In all surgical specimens, irrespective of original tumor histology and radiation modal-
ities, H&E staining showed marked angiogenesis and reactive gliosis at the boundary between the apparent necrotic area and the normal brain. We described this border zone as the “peri-necrotic” area. The most pro-
minent vasculatures in this area consisted of a thin endothelium, mimicking venules, which is identified as telangiectasia. Immunohistochemistry indicated that VEGF was produced mainly in the reactive astrocytes in this peri-necrotic area. There was no evidence of marked immunoreactivity of VEGF either in the center of the necrotic tissue nor in the intact brain. Clinically, all RN cases treated by bevacizumab and removal of necrotic tissue showed the rapid shrinkage of the pre-edema lesion. DISCUSSION: These findings suggest that VEGF in the peri-necrotic area might be a cause of angiogenesis and the subsequent peri-lesional edema typically found in radiation necrosis of the brain. CONCLUSION: During the radiation phase of RN, anticoagulants may be effective for preventing microcirculation by preventing such small venules and arterioles from the thrombotic obstruction. However, in the later advanced phase of RN, medical treat-
ment with anti-VEGF antibody, bevacizumab or surgical removal of the necrotic tissue and associated peri-necrotic area may serve to decrease this edema and provide improved symptomatic improvements, because of the effect of reducing VEGF in this area.

**NEURO-OLOGY-IM II**

**O.43. HOT SPOTS IN 1H-FET-PET DELINEATE MALIGNANT TUMOR PARTS WITHIN SUSPECTED WHO GRADE II GLIOMA**

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OBJECTIVE: This prospective study correlates metabolic maps of intra-
tumoral [F-18]fluorodeoxyribose (FET) uptake kinetics with detailed his-
topathology and molecular genetic profiling in untreated gliomas with magnetic resonance imaging (MRI)-based suspicion of a WHO grade II glioma. Special attention was set on diagnostic accuracy of FET-PET in noninvasive delineation of an anaplastic focus. METHODS: Individual maps of FET uptake kinetics were generated and metabolic hot spots were outlined three dimensionally. Novel 1H-FET-PET-guided serial stereo-
tactic biopsy procedures were found suitable for stepwise histopatholog-
ical and molecular genetic evaluation. Histopathology was done according WHO criteria by independent observers. O-Methylguanine-
DNA methyltransferase (MGMT) promoter methylation was determined by methylation-specific polymerase chain reaction/sequencing and isoci-
date dehydrogenase (IDH1/2) mutations by immunohistochemistry analy-
sis, respectively. RESULTS: A total of 373 biopsy samples from 55 consecu-
tively enrolled patients were analyzed. In 24 patients, the WHO grade II glioma was diagnosed. Homogeneous metabolic kinetics was significantly linked to histopathological homoegenity in 40 patients. In 15 patients, a hetero-
geneous FET uptake kinetic was found throughout tumor volumes and a progression of homogenization with grade III histopathology was confirmed. FET-PET analysis reached a sensitivity of 92% and specificity of 82% in determination of an anaplastic focus. Eleven out of 14 patients with heterogeneous histopathology were MGMT methylated and 9 tumors showed IDH1/2 mutations. Both mutations are homogeneously distributed throughout each tumor irrespective of an analy-
plastic focus. CONCLUSION: Homogeneous or heterogeneous glioma histology can be precisely delineated by dynamic FET-PET evaluation; an anaplastic focus can be reliably identified using this new imaging modality with implications for prognostic evaluation, biopsy planning, and individualized treatment strategies.
O.44. LANGUAGE MAPPING FINDINGS AND CORRELATION WITH DTI–FT DATA DURING SURGICAL REMOVAL OF LESIONS INVOLVING LANGUAGE AREAS OR PATHWAYS
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Surgical resection of lesions involving language areas or pathways requires intraoperative identification of functional cortical and subcortical sites to effectively and safely guide resection. Diffusion tensor imaging (DTI) and fiber tractography (FT) are magnetic resonance (MR) techniques based on the concept of anisotropic water diffusion in myelinated fibers, which allow a three-dimensional reconstruction and visualization of white matter tracts, and provide information about the relationship of these tracts with the tumor mass. We have routinely used DTI–FT to reconstruct various tracts involved in the language system [superior longitudinal (SLF), inferior fronto-occipital (IFO), inferior longitudinal (ILF), uncinate (UNC), premotor fibers] in a series of 305 patients with gliomas (mostly low grade) involving the language areas or pathways. DTI–FT information was loaded into the neuronavigational system and combined intraoperatively with those obtained with direct electrical stimulation (DES). In this work, we report the results of such experience, describing the findings for each tract and discussing technical aspects of the combined use. Large part of SLF was located inside the tumor mass and highly infiltrated by it, and can be safely resected because not functional. IFO was a discrete fasciculus and, when identified intraoperatively, was functional in most of the cases. ILF was located at the lateral portion of temporal tumors and identified as a separate tract in functional in small tumors. The temporal portion on UNC could be removed, whereas the frontal portion had to be preserved to keep language functional integrity. Premotor face fibers must be reconstructed, identified, and preserved intraoperatively to avoid anarthria. Tract identification was associated with a 79% chance to develop early postoperative deficits. The rate of definite deficits (at 1 mo) was <2%. The rate and speed of recovery in the postoperative period correlated with the subcortical organization of some of the tracts, such as the SLF, and could be predict preoperatively. The combined use of DES and DTI–FT allowed to effectively and safely trace language tracts, reduced duration of surgery, patient fatigue, and kept a high rate of patient functional integrity.

O.45. USEFULNESS OF NMR-BASED METABOLICOMICS (METABOLOME) USING THE ANALYSIS OF WATER AND LIPID SOLUBLE METABOLITES AS THE PREDICTIVE FACTORS OF MALIGNANT-TYPE MENINGIOMAS
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PURPOSE: In meningiomas which are considered to be benign brain tumors, there are malignant-type tumors. Most of these malignant-type meningiomas are histologically diagnosed anaplastic or atypical ones. However, some of malignant-type meningiomas show poor clinical courses, although histological diagnoses are benign. It is difficult to distinguish this specific group from usual benign-type meningioma. Therefore, we tried to gain characteristic extraction by the metabolite expression profiling using nuclear magnetic resonance (NMR)-based metabolomics (comprehensive metabolite analysis). METHODS: We extracted water and lipid soluble metabolites from recent frozen surgical specimens which are 31 meningiomas, including 2 anaplastic, 1 atypical, and 2 malignant-type cases, and measured 1H-NMR spectra. Then, we did power of FLT–PET for predicting survival. RESULTS: Twenty-two patients were histopathologically diagnosed as malignant meningiomas (mostly low grade) involving the language areas or pathways. The mean overall survival was 411 days (min. 51 days, max. 881 days, SD 262) and mean age was 52 years (range 35–67 years), and 20 patients were male. The rate and speed of recovery in the postoperative period correlated with the subcortical organization of some of the tracts, such as the SLF, and could be predict preoperatively. The combined use of DES and DTI–FT allowed to effectively and safely trace language tracts, reduced duration of surgery, patient fatigue, and kept a high rate of patient functional integrity.

O.46. INTRA- AND INTEROBSERVER AGREEMENT IN VOLUMETRIC ASSESSMENT OF GliOBlastoma MULTIFORME RESection
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OBJECTIVE: The aim of this study was to analyze intraobserver and interobserver agreement of manual segmentation as a method for volumetric assessment of glioblastoma multiforme (GBM) resection. METHODS: Three observers performed volumetric assessment of preoperative tumor volume (PreTV) and postoperative tumor volume (PostTV) by manual segmentation on contrast-enhanced T1-weighted magnetic resonance imaging (MRI) data sets of patients. Measurements were repeated after an interval of minimum 2 weeks. Intraobserver and interobserver agreement was high for PreTV (ICC = 0.99), PostTV (ICC = 0.93 – 0.94) and RTV (ICC = 0.89 – 0.94). Interobserver agreement is high for PreTV (ICC = 0.97), but low for PostTV (ICC = 0.54) and RTV (ICC = 0.52). CONCLUSION: Volumetric assessment of GBM resection seems to offer high intraobserver agreement, but low interobserver agreement. The results suggest that segmentation methods used to estimate the PTV might be unreliable. Further research is needed before this method can be used as a valid endpoint for clinical studies.

O.47. 18F-FLOuROThYMIDINE (FLT)–POsITRON EMISSION TOMOGRAPHy TO DETERMINE THE Proliferative Tumor Volume in HIGH-GRADE GLIOma and Correlation With Survival
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INTRODUCTION: 18F-fluorothymidine (FLT) is a tracer for positron emission tomography (PET) depicting tumor cell proliferation. Quantitative analysis by calculating the maximum standardized uptake value (SUVmax) has been shown to correlate with the Ki-67 index, time to progression, and overall survival. For estimating the proliferative tumor volume (PTV), different PET segmentation methods can be used. The aim of this study was to identify the method that best predicts overall survival. MATERIALS AND METHODS: 30 patients with glioblastoma multiforme underwent a preoperative computed tomography (CT) and FLT–PET scan. The SUVmax of all tumors was calculated after manual delineation of the PTV on the co-registered CT and FLT–PET scans. Three different segmentation methods for estimating the PTV were used. Tumor resection with survival may be unreliable. More research is needed before this method can be used as a valid endpoint for clinical studies.

O.48. EARLY PROGRESSION BETWEEN SURGERy AND ADJUVANT CHEMO-RADIoThERAPY IN GLIOBLASTOMA
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BACKGROUND AND PURPOSE: The assessment of early progression after surgery and before adjuvant treatment in glioblastoma (GBM) may (i)
SUPPORTIVE CARE

O.49. IDENTIFYING CLINICAL DEPRESSION IN PATIENTS WITH BRAIN TUMORS
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BACKGROUND: Depression is under-recognized in patients with brain tumors. A standardized psychiatric interview is the “gold standard” method of diagnosing clinical depression. We studied the frequency of depression and clinical associations of DSM-IV major depressive disorder (MDD) in adults with glioma. METHODS: This was a prospective, twin-centre, longitudinal cohort study of adults with newly diagnosed primary cerebral glioma. All sub- jected to a baseline psychiatric interview. METHODS: This was a prospective, two-center, longitudinal cohort study of adults with newly diagnosed primary cerebral glioma. All subjects had a structured psychiatric interview to diagnose or exclude MDD. Data are presented from the first two time-points: T1 (shortly after starting radiotherapy, or equivalent) and T2 (3 months later). RESULTS: We examined 155 patients at T1 and 108 at T2. Fifty-seven percent patients were male. Mean age was 54 years, 86% had high-grade glioma. 78% received radical radiotherapy, and the median KPS was 90. We diagnosed MDD in 20 patients at T1 (12.9 ± 5.3%) and in 16 cases at T2 (14.8 ± 6.7%). Of the 20 patients with MDD at T1, 2 had recovered by T2; 7 continued to have MDD and 11 dropped out of the study. Nine new patients developed MDD by T2. These changes underlay the overall tendency for the point prevalence of MDD to increase over time (P = .065, McNemar test). We found univariate associations (all χ², P < .05) between MDD and functional impairment (KPS ≤ 70%), current steroid use, recent surgery, depression, anxiety disorders, and variable preceding prescription and/or high emotional distress (NCCN distress thermometer score ≥4/10). In multivariate analysis, MDD was independently associated with functional impairment and high emotional distress (logistic regression χ² P = .001, R² = .294). CONCLUSIONS: This is the first longitudinal study of depression in glioma patients using clinical interview. Major depression afflicted nearly 1 in 5 individuals during the study period. MDD persisted at reassessment after 3 months, and new cases occurred over time. These with MDD were different in the longitudinal study. Functional impairment and emotional distress were independent risk factors. Clinicians should screen for depression in patients with glioma who report high distress on the NCCN distress thermometer, or with nondepressed glioma patients compared with a structured psychiatric interview. SUPPORTIVE CARE

O.50. PSYCHOLOGICAL FACTORS OF THE RETARDATION OF MENTAL DEVELOPMENT IN CHILDREN WITH RECURRENT BRAIN TUMORS
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BACKGROUND: The survivors of recurrent childhood cancer achieve fewer milestones than their peers with respect to autonomy development, social development, and psycho-sexual development or achieve, the milestone when they are older than their peers. There is the evidence of retardation of mental development in children with brain tumours as the result of not only complex consequences of the brain tumors and their treatment but the psycho-social situation of development, social situation. This is the challenge for the complex use of the multidisciplinary psychological methods – neuropsychological, clinical psychology, psycho-omatic, family psychology. METHODS: The results of the complex testing of 50 children of the age 10–16 years old and their mothers were examined (with spinal brain tumors n = 10; with head brain n = 40). The Luria’s method of complex neuropsychological diagnostics (for children), projective drawings, Children Apperceptive Test: questionnaire of Parental Attitude, Spilberger test, and questionnaire of Posttraumatic Growth (for mothers) were used as well as interview. RESULTS: The most sensitive for the brain functions disorders in children is neuropsychological testing of visual-spatial and visual-constructive functions (in 40% of children with head brain tumors). The parental attitude to the child, actual mothers‘ emotional state, intention to continue education, opportunity of social contacts are the most significant prognostic factors of the mental development and compensation of the neuropsychological disorders excluding visual-spatial and some other. CONCLUSIONS: There is the need of special educational and psycho-social programs for the children with recurrent brain tumors and their families.

O.51. A HADS DEPRESSION SUBSCALE SCORE ≥ 8 CAN HELP SCREEN FOR DEPRESSION IN ADULTS WITH PRIMARY GLIOMA
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BACKGROUND: No study has validated a screening tool for the purposes of diagnosing depression in adults with glioma. We examined whether the hospital anxiety and depression scale (HADS) discriminates between depressed and nondepressed glioma patients compared with a structured psychiatric interview. METHODS: This was a prospective, two-center, longitudinal cohort study of adults with newly diagnosed primary cerebral glioma. All subjects completed the 7-item depression subscale of the HADS (HAD-D, score range 0–21) and received a “gold-standard” structured interview to diagnose or exclude major depressive disorder (MDD). Data are presented from the first two time-points: T1 (shortly after starting radiotherapy) and T2 (3 months later). Analysis was done by receiver operating characteristic curves. RESULTS: We examined 133 patients at T1 and 90 at T2. Of them, 57% were male. Baseline sample characteristics were: mean age 54 years, 84% had high-grade glioma and 80% received radical radiotherapy. The HAD-D showed good discrimination both at T1 (AUC = 0.93) and at T2 (AUC = 0.98). At T1, a cut-off of ≥ 7 had 0.93 sensitivity and 0.89 specificity for MDD (PPV = 54%; NPV = 99%, LR + = 9.1). With a cut-off ≥ 8, sensitivity was 0.73 and specificity was 0.92, but predictive values were similar (PPV = 55%; NPV = 96%, LR + = 9.6). At T2, a cut-off of ≥ 8 had 0.92 sensitivity and 0.92 specificity for MDD (PPV = 67%; NPV = 99%; LR + = 11.8). CONCLUSIONS: Depression in glioma is potentially treatable. The HAD-D may be a useful screening tool. It discriminated well between depressed and nondepressed patients in our cohort of 133 well-functioning adults with primary glioma. A cut-off of ≥ 8 may be favored because this threshold functioned well with MDD at every time-point studied. This score is also consistent with established cut-offs in other populations of medically ill patients and may be more familiar to clinicians. The higher PPV at T2 may represent a lower “background” level of distress as patients adjust to their diagnosis. The HAD-D can be completed easily by glioma patients receiving treatment, but does have practical limitations. The paper is not easily completed by patients with dysphasia, hemianopia, neglect, or hemiparesis. The impact of cognitive impairment and the reproducibility and internal consistency of the
O.52. SCREENING FOR COGNITIVE IMPAIRMENT IN PRIMARY BRAIN TUMOR: IS THE MONTREAL COGNITIVE ASSESSMENT A MORE SENSITIVE TOOL THAN THE MINI MENTAL STATE EXAMINATION?
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BACKGROUND: The cognitive sequelae of primary brain tumor (PBT) and its associated treatments are well established. Although the mini mental state examination (MMSE) is widely used as a screening measure to detect cognitive impairment, it has limitations. This study aimed to compare a newer and potentially more sensitive screening tool, the Montreal Cognitive Assessment (MoCA), to the MMSE in a neuro-oncology population.

METHODS: A series of 40 patients with histologically confirmed PBT from Liverpool Hospital, Sydney, were recruited over a 7-month period. Both the MMSE and MoCA screening tools were administered to all patients to assess the presence of cognitive impairment. Clinical and socio-demographic data were also documented. RESULTS: There were 21 males and 19 females, with mean age of 51.3 years (SD = 15.9) and median time since diagnosis 13 months (IQR 4.0–22.8). The tumor diagnoses were: high-grade n = 11 (28%), low-grade n = 11 (28%), and benign tumors, including pituitary adenoma and meningioma, n = 18 (44%). A total of 16 patients underwent resection only, 11 patients received both surgery and radiotherapy (RT), while n = 9 were treated with a combination of surgery, RT, and chemotherapy. Thirteen patients (33%) had a history of epileptic seizures and 14 (35%) were taking anti-epileptic medications at time of assessment. Only 8 (20%) patients were taking prescribed steroids. In the assessment of cognitive function, 28 patients (70%) were deemed impaired using the MoCA, compared with 15 (38%) using the MMSE. Of the 34 patients with a normal MMSE, 22 of 40 (55%) demonstrated cognitive impairment according to the MoCA. There were no patients with a normal MoCA score who also had an impaired MMSE score. Notably, of the 28 patients with an abnormal MoCA, 22 of 28 (79%) had a normal MMSE. CONCLUSIONS: These preliminary results suggest that the MoCA has demonstrated utility as a brief cognitive screening tool and is more sensitive in detecting cognitive impairment than the MMSE in a population of primary brain tumor patients.

O.54. EPILEPSY AT THE END OF LIFE IN MALIGNANT GLIOMAS
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Epilepsy is common in patients with brain tumors. Frequently, an epilepsy aura is the first symptom of the cerebral lesion, but epileptic seizures may also occur. More than one-third of cases with primary brain tumors present with epileptic seizures, and the incidence at diagnosis varies with histological type and location. Another 10%–30% of patients develop epilepsy in the course of their disease. Patients who present with seizures at the first sign of a malignant glioma are at increased risk of recurrent seizures despite treatment with antiepileptic drugs. However, little is known about the incidence of epilepsy in the last stage of disease and at the end of life of brain tumor patients. We retrospectively analyzed the incidence of seizures in the last months of life in a series of patients affected by malignant gliomas assisted at home during all the course of disease until death with a comprehensive neuro-oncological home care program. One hundred fifty-seven patients affected by malignant gliomas were included in this study. Epilepsy at onset was present in 52 (33.1%) patients; 33 (21%) patients presented late onset epilepsy (during the course of disease and before the last months of life); 58 patients (37.6%) presented epilepsy in the last month before death. In 9 cases, seizures occurred in the last month of life, in 19 patients seizures were present in the last month of life, whereas in 124 patients seizures occurred in previous episodes. The incidence of seizures in the last month of life was higher in patients presenting late onset epilepsy (25 of 53, 75.8%) with respect to the group of patients presenting early onset (25 of 52, 48.1%). In the group of patients not presenting previous episode (72 of 137, 46%), the incidence of epilepsy at the end of life was 12%. In this group, 47 patients received anticonvulsant prophylactic treatment and 25 not. The occurrence of seizures was not correlated with anticonvulsant treatment. Anticonvulsant treatment at the end of life or brain tumor patients presents particular concerns with respect to other stages of disease, given the frequent difficulty to swallow oral therapy in patients dying. Oral treatment needs to be changed in advance with intramuscular or subcutaneous administrations. More studies should be addressed to the issue of epilepsy at the end of life in brain tumor patients.

O.53. HOW TO BEST MEET THE NEEDS OF PATIENTS WITH A GLIOBLASTOMA AND THEIR FAMILIES: SCREENING FOR PSYCHOSOCIAL DISTRESS OR A STANDARD CONSULTATION WITH A SOCIAL WORKER AS PART OF THEIR MEDICAL TREATMENT?
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PURPOSE: The aim of the study was to evaluate the need for integrated psychosocial counseling as part of the treatment plan in patients with a high-grade glioma and to investigate whether standard counseling leads to improved psychosocial support for the patients and their family.

MATERIALS AND METHODS: Patients with a glioblastoma multiforme (GBM) are potentially faced with more physical, psychological, and social problems because of the nature of their illness. Patients are aware of the fact that they have an aggressive tumor with a limited lifespan. Owing to the effect on the cerebral function, not only the patient can experience a great loss of health and functioning, but the disease also has an obvious social impact on family life. The family often needs to take on new responsibilities and has to face at the same time the fear of losing their loved one.

RESULTS: Of 123 patients treated for a primary GBM between 2006 and 2010, 101 (82%) patients were referred for standard counseling at the beginning of the radiotherapy. Of the 101 referred patients, 43 (42.6%) were further actively accompanied, whereas for 58 (57%) patients there was no further necessity of psychosocial support. Nevertheless, the baseline counseling was experienced in a positive way. Follow-up counseling ranged between 4 and 14 sessions during and after radio/chemotherapy per patient depending on the needs. Patients with devastating effects of the brain tumor and an accompanying large impact on their personality and abilities need of continued support. CONCLUSIONS: If counseling is integrated into the treatment plan, the hurdle of seeking advice is lower and support is easier accepted (majority of 82%). There is a large need for psycho-social counseling for patients harboring a GBM and should therefore be part of the overall treatment plan to improve quality-of-life for patients and their families.

O.55. INF-β SENSITIZES GLIOMA CELLS TO TEMOZOLOMIDE IN AN MGMT- AND P53-INDEPENDENT MANNER
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The alkylating agent temozolomide is the first drug to significantly prolong progression-free and overall survival when used in combination with surgery and radiotherapy in newly diagnosed glioblastoma. Glioma cell sensitivity to temozolomide is strongly associated with promoter methylation of the O6-methyl guanine transferase (MGMT) gene. Further, in vitro studies
O.58. NON-R132 MUTATIONS IN IDH1 IDENTIFY A NOVEL SUBGROUP OF LOW-GRADE GLIOMAS WITH DISTINCTIVE LOCATION, INfiltrATIVE BEHAVIOR, DISMAL OUTCOME, AND UNIQUE MOLEcULAR PAtTERnS

INTRODUCTION: Chromosomes 1p and 19q deletions and TP53 mutations represented the 2 main genetic alterations described in low-grade gliomas (LGGs). Interestingly, non-R132 IDH1–mutated tumors and TP53 mutations and 1p19q codeletion were found to be exclusive. The predictive impact of these two genetic alterations on outcome in LGG is still source of controversies. However, LGGs harboring 1p19q deletion and no TP53 mutations have been reported to have a better prognosis than TP53-mutated tumors and 1p19q-intact LGGs. In 19q, intriguingly, no data are available on the intermediate group of LGGs harboring a “null” phenotype (no TP53 mutation and no 1p19q codelletion). Recently, mutations of sod3 and dehydrogenase enzyme isoforms 1 (IDH1) and 2 (IDH2) have been found in a large proportion of LGGs. To date, few data are available regarding the prognostic impact of IDH1 and 2 mutations in a homogeneous LGG population. We address here, for the first time, a comprehensive analysis of the segregation of non-R132 mutations in IDH1 in distinct molecular subtypes of LGGs and report the clinical outcome and radiological features of this novel subgroup of tumors. METHODS: Patients (48) treated at Timone University Hospital, Marseille, France, between 2002 and 2008 were selected from the following criteria: histological diagnosis of WHO LGG was available para- or embedded tissue; available magnetic resonance imaging data at diagnosis; clinical and follow-up data from the database; and written informed consent. The pathology of all tumors was centrally reviewed by two independent neuropathologists. Complete physical and neurologic examinations, KPS score, and MRI scan data were collected at the time of diagnosis. MRI data assessed by two neuroradiologists included tumor size, midline mass effect, heterogeneity, infiltration, contrast enhancement, and location. MRI-based extent of surgery was assessed at 3 months post-op. RESULTS: Sex ratio was 1.29 (27 men and 21 women) and median age 59.8 years (range, 22–71 years). A total of 41 mutations in IDH1 were identified (85.4%) and 2 mutations in IDH2. Five-year overall survival was 86.6 vs 60 months in patients with R132 IDH1 and non-R132 IDH1 mutated tumors, respectively (P < .01). Furthermore, non-R132 IDH1–mutated tumors had a no mutation in TP53 and no codelletion of 1p19q in 71.4% of cases compared with 8.3% in non-R132 IDH1–mutated tumors (P < .001). Finally, 7 of 7 (100%) of the non-R132 IDH1–mutated tumors were paralimbic and displayed an infiltrative radiological phenotype compared with 9 of 41 (21.9%) patients of R132 IDH1–mutated tumors (P < .0001). CONCLUSION: Non-R132 mutations in IDH1 identify a novel subgroup of LGGs with distinctive topography, radiological aspect, and dismal outcome. Furthermore, non-R132 mutations in IDH segregate in a distinct molecular subtype of LGGs.

O.59. DYNAMIC HISTORY OF LOW-GRADE GLIOMAS TREATED WITH FIRST-LINE PCV CHEMOTHERAPY

The objective of this retrospective study was to evaluate the impact of first-line PCV chemotherapy on low-grade glioma (LGG) growth. For this purpose, the mean tumor diameter (MTD) of 21 LGGs was evaluated on serial magnetic resonance images before (n = 13), during, and after PCV onset (n = 21). During PCV, a decrease of the MTD was observed in all patients. After the end of PCV, though at a slower rate, a continuing decrease of the MTD was observed in 20 out of 21 patients. Median duration of this
persistent decrease was 2.7 years (0–7 years). According to MacDonald’s criteria, the rates of partial and minor responses were 44% at the end of PCV (6% partial and 38% minor responses), but 75% at the time of maximal tumor response, after a median of 3.4 years following PCV onset (43% partial and 32% minor responses). A persistent and prolonged decrease of LGGs volume (>2 years) was observed in 60% of the patients despite no more chemotherapy was administered. These results challenge the current view that a prolonged chemotherapy treatment is necessary to achieve a prolonged response and also to raise the issue of the mechanisms involved in the persistent tumor decrease once chemotherapy is stopped.

O.06. WHICH MOLECULAR SIGNATURES PREDICT PROGRESSION-FREE SURVIVAL AFTER SURGERY ALONE IN PATIENTS WITH LOW-GRADE GLIOMAS?

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PURPOSE: TP53 mutations, 1p/19q codeletions, O6-methylguanine- methyltransferase (MGMT) promoter methylation, and isocitrate dehydrogenase (IDH)-1/2 mutations have been proposed to be associated with outcome in patients with low-grade gliomas. Here we sought to clarify whether these molecular signatures reflect a favorable natural course or a synergistic response to radiotherapy or chemotherapy. EXPERIMENTAL DESIGN: Ninety-three patients with diffuse astrocytoma WHO grade II (A-II, n = 42), oligoastrocytoma (OA-II, n = 24), or oligodendroglioma (O-II, n = 27), who had not received radiotherapy or chemotherapy after their first operation, were monitored until the end of follow-up (n = 59) or until the first progression (n = 39), with a median follow-up of 6.1 years. Tumor tissues were analyzed for TP53 mutations, 1p/19q status, MGMT promoter methylation, and IDH-1/2 mutations. RESULTS: The estimated median progression-free survival (PFS) was 3.9 years (95% CI 2.9–4.9). Fifty-four patients progressed and 17 patients died. The relative frequencies were 27.0% (24/89) for TP53 mutations, 41.1% (37/90) for 1p/19q codeletions, 43.8% (39/89) for MGMT promoter methylation, and 81.5% (75 of 92) for IDH-1/2 mutations. TP53 mutations were uncommon in patients with 1p/19q codeletions. None of the molecular markers was prognostic for PFS, using multivariate adjustment for histology, extent of resection, age, and gender. Similarly, none of the parameters predicted survival from first progression. Solely IDH-1/2 mutations were associated with prolonged overall survival. CONCLUSIONS: None of the studied parameters is a sensitive prognostic biomarker in patients with grade II gliomas who do not receive radiotherapy or chemotherapy after surgery. IDH-1/2 mutations were confirmed to predict longer survival.

O.06.1 A COMPREHENSIVE STUDY OF THE ASSOCIATION BETWEEN THE EGFR AND ERBB2 GENES AND GLIOMA RISK

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BACKGROUND: Glioma is the most common type of adult brain tumor and glioblastoma, its most aggressive form, has a dismal prognosis. Receptor tyrosine kinases such as the epidermal growth factor receptor (EGFR, ERBB2, ERBB3, and ERBB4) family, and the vascular endothelial growth factor receptor (VEGFR) play a central role in tumor progression. We investigated the genetic variants of EGFR, ERBB2, VEGFR, and their ligands, EGF and VEGF, on glioma and glioblastoma risk. In addition, we evaluated the association of genetic variants of a newly discovered family of genes known to interact with EGFR: LRIG2 and LRIG1 with glioma and glioblastoma risk. METHODS: We analyzed 191 tag single nucleotide polymorphisms (SNPs) capturing all common genetic variation of EGFR, ERBB2, LRIG2, LRIG1, VEGF, and VEGFR2 genes. Material from 4 case-control studies with 725 glioma patients (329 of whom were glioblastoma patients) and their 1610 controls was used. Haplotype analyses were conducted using SAS Genotyping software. FINDINGS: Fourteen of the SNPs were significantly associated with glioma risk at P < .05, and 17 of the SNPs were significantly associated with glioblastoma risk at P < .05. In addition, we found that one EGFR haplotype was related to increased glioblastoma risk at P = .009, odds ratio [OR] = 1.67 (95% confidence interval (CI): 1.14, 2.45). The Bonferroni correction made all P-values nonsignificant. One SNP rs4947986 next to the intron/exon boundary of exon 7 in EGFR, was validated in an independent data set of 713 glioblastoma and 2236 controls, OR = 1.42 (95% CI: 1.06, 1.91). INTERPRETATION: Previous studies show that regulation of the EGFR pathway plays a role in glioma progression, but the present study is the first to find that certain genotypes of the EGFR gene may be related to glioblastoma risk. Further studies are required to revalidate these findings and evaluate the functional significance.

O.06.2 COGNITIVE DEFICITS IN PATIENTS WITH GLIOMAS IN ELOQUENT AREAS BEFORE AND AFTER AWAKE SURGERY

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INTRODUCTION: Cognitive performance is an important outcome measure of brain tumor treatment, as neuropsychologic deficits have an impact on quality of life. Previous neuropsychologic studies found that the majority of glioma patients have deficits in one or more cognitive domains such as language, executive functions, verbal and nonverbal memory, and processing speed. The presence and severity of cognitive disorders is one of the main factors in the decision procedure about awake operations. However, the effect of surgery on these cognitive deficits still needs further investigation. In the present exploratory study, a comprehensive assessment of cognitive functioning was performed before and after awake craniotomy. METHODOLOGY: Cognitive functioning of patients with gliomas in language or motor areas (n = 29) before and 3 months after awake craniotomy was assessed with Aachener aphasia test; Boston Naming Test; Verbal (Letter and Category) Fluency; WordMemory; Stroop Color-Word Test; Trail Making Test (TMT) A&B; Orientation and Clock drawing. Within 4 days after surgery, a neuropsychologic examination was carried out to screen for functional deficits. Change in cognitive performance was related to the pathology (WHO grade), type, volume, and location of the tumor. RESULTS: Before surgery, results on BNT, WordMemory, Verbal Fluency, Stroop Test, and TMT deviated from performance of healthy adults (P < .01). Three months after surgery, the same profile of deficits was found. Compared with preoperative assessment, performance slightly decreased on letter fluency (P = .015), category fluency (P = .036) and TMT B (P = .044). Patients with clinically observed language deficits in the direct postoperative stage (62%) consistently declined more on these tests than patients with no direct postsurgical language impairment. The pathology, type, volume, and localization of the tumor did not affect the change of cognitive performance. Discussion: Data about cognitive functioning of patients with gliomas in eloquent areas before and after awake surgery are scarce. The results of our study indicate that the global cognitive profile of glioma patients does not considerably change after surgery. The further decline of 3 months after surgery on some language and executive tasks appears to be related to the occurrence of language deficits in the direct postoperative stage. To observe the long-term cognitive outcome, a 1-year follow-up is performed. Furthermore, a larger group of patients will be investigated with a protocol containing more nonverbal tests, to discern the influence of cognitive disorders (e.g., memory, executive functions) on performance of this patient group.

O.06.3 QUALITY OF LIFE IN HIGH-GRADE GLIOMA PATIENTS AND THEIR RELATIVES IN THE END-OF-LIFE PHASE

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INTRODUCTION: Despite intensive treatment with surgery, chemotherapy, and radiotherapy, patients with high-grade glioma (HGG)
eventually experience tumor recurrence up to a point that no further curative treatment options are available. From that moment on, only supportive treatment is given. In this end-of-life phase, maintaining acceptable quality of life (QOL) as long as possible is the main goal. Previous studies demonstrated that symptom burden increases as death approaches and it is assumed that symptom burden negatively affects QOL of both patients and their relatives. However, until date, no quantitative information is available in the end-of-life phase. Our study was to describe QOL toward the end of life in HGG patients and their relatives. METHODS: We identified a cohort of 148 deceased HGG patients diagnosed in 3 Dutch hospitals in 2005 and 2006. Patients and the patients’ caregivers were identified through a cohort registry and invited to participate in the study and asked to fill in a questionnaire regarding the end-of-life phase of the specific patient. In this study, the end-of-life phase was divided in the last 3 months before death and the last week before death. Physicians of 93 patients (63%) participated in the study and answered questions concerning symptoms in the end-of-life phase. Relatives of 127 patients could be traced, and 68 relatives (54%) participated in the study. The questionnaire for relatives covered questions regarding symptoms and QOL issues of the patient as well as questions about the relatives’ QOL in the last 3 months of the patients’ life. Data were recorded descriptively. RESULTS: Both physicians and relatives reported lost of consciousness (34%–45%), confusion (53%–75%), incontinence (31%–55%), headache (31%–45%), and seizures (38%–40%) as most important symptoms in the last 3 months of life. Symptom burden increased in the last week of life. According to their relatives, 90% of HGG patients were limited in social activities and would probably have rated their general QOL as poor. QOL of the relatives in the last 3 months of the patients’ life was also compromised: 85% of relatives were limited in social activities and 65% felt burn-out. Moreover, in 60% of the cases, the disease disrupted family life and, in 20% of the cases, the disease perturbed the relationship between the patient and his/her partner. CONCLUSION: Symptom burden is high, and QOL is rated poor in the end-of-life phase of HGG patients. Informal caregivers report relatively low QOL for themselves as well as high levels of stress. This knowledge could be used to develop specific protocols and interventions to improve the QOL of glioma patients and their relatives.

O.65. PREDICTORS OF QUALITY OF LIFE OF PARTNERS OF HIGH-GRADE GLIOMA PATIENTS

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Although primary brain tumors account for only 2% of all cancers, they may severely disrupt a patient’s daily life activities because of the multiplicity and severity of the symptoms associated with this disease. The physical, cognitive, and behavioral symptoms caused by the tumor and its treatment do not only affect the patient, but also the ones living with the patient. Their new role as caregivers, partners of these patients may experience a great deal of stress and caregiver burden, negatively affecting their quality of life (QOL) and thus their ability to cope with their new caregiver tasks. The present study aims at (i) evaluating QOL of partners of high-grade glioma patients and (ii) determining which partner and patient-related factors affect partners’ QOL. Forty-eight patient–caregiver dyads participated in this study. Most patients were diagnosed with a GBM (n = 32). The remainder had anaplastic oligoastrocytomas (n = 9), anaplastic astrocytomas (n = 2), or WHO grade III oligoastrocytomas (n = 2). Partners were somewhat more often female (n = 29) than male. Mean age of the partners was 51.0 years (SD = 11.2). All partners filled out extensive questionnaires concerning their QOL (SF36), feelings of depression and anxiety, (HADS), and caregiver mastery (CMS). Additionally, partners reported their perceptions of patients’ health-related quality of life (HRQOL) (SF36), neurological functioning (BCM20), and cognitive functioning (MOS). Compared with general population controls, matched for age, sex, and educational level, caregiving partners reported better physical functioning (P = .000), but poorer mental functioning (P = .002). Expectantly, partners’ feelings of caregiver mastery (P = .000) and feelings of anxiety and depression (P = .000) strongly predicted the physical functioning of the partners, whereas mental functioning was not predictive of partners’ QOL, except for caregivers of patients with newly diagnosed gliomas (n = 19) whose mental functioning also predicted the mental functioning of the partners, however, to a lesser extent. These results suggest that partners, in their new role as caregivers of high-grade glioma patients experience poorer mental functioning. These limitations in mental functioning are most strongly predicted by their own feelings of depression and anxiety and feelings of caregiver mastery. Health-related quality of life of the patient and their neurological functioning also predicted the mental functioning of the partners, however, to a lesser extent. These results suggest that partners, in their new role as caregivers of high-grade glioma patients, might benefit from psychological interventions aimed at the enhancement of their quality of life.

O.66. GLOIOBLASTOMA IN ELDERLY PATIENTS: HEALTH-RELATED QUALITY OF LIFE (HRQOL) IN A RANDOMIZED TRIAL COMPARING 6-WEEKS VS TEMOZOLOMIDE CHEMOTHERAPY (TMZ) WITH HYPOFRACTIONATED RT OVER 2 WEEKS VS TEMOZOLOMIDE CHEMOTHERAPY (TMZ)

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BACKGROUND: Despite advances in treatment, survival of patients with GBM over 60 years is still often less than 1 year. In the perspective of a short expected survival, the quality of the remaining life and the effects of therapy on health-related quality of life (HRQoL) should be given special emphasis when recommending treatment for the individual patient. Several studies have focused on survival of the elderly, but few data are available on HRQoL for different treatments. In a randomized trial, we compared survival and HRQoL for 3 treatment options, 6 weeks of RT, vs hypofractionated RT, or chemotherapy with TMZ.

MATERIALS AND METHODS: Newly diagnosed GBM patients, age
O.67. HAVE CLINICAL FEATURES AND TREATMENT OUTCOME OF 166 PATIENTS WITH NEUROLYMPHOMATOSIS (NL) CHANGED OVER A PERIOD OF 36 YEARS? ASSESSMENT OF THE CONTEMPORARY INTERNATIONAL PRIMARY CNS LYMPHOMA COLLABORATIVE GROUP (IPCG) SERIES AND LITERATURE CASE REVIEW

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Neurolymphomatosis is a rare clinical entity characterized by infiltration of peripheral nerves, root nerves, plexus, or cranial nerves by malignant lymphocytes. The IPCG retrospectively analyzed 50 patients (Group A) assembled from 12 centers in 5 countries over a 16-year period. As 70% of patients in this series were diagnosed during the last 8 years, we tried to compare the contemporary series with literature review.

The latter included case reports of 44 patients published from 2001 to 2008 (Group B) which corresponds to the period of diagnosis of the greater fraction of our patients, and 72 patients (Group C) identified earlier during a 28-year period (1972–2000). Median age (55.5 years) and median number of anatomic structures affected (2) were similar among Groups A, B, and C. The predominant tumor type was B-cell, whereas T-cell-type tumor occurred in 10%, 23%, and 5% of Groups A, B, and C, respectively. The predominant malignant cell type was B-cell, whereas T-cell-type tumor occurred in 10%, 23%, and 5% of Groups A, B, and C. In our series, NL affected more than 1 anatomic structure in 58% of patients with peripheral nerves, being the most frequently involved site (60%) while spinal, cranial nerve, and peripheral plexus infiltration occurred at a similar rate (40%–48%). Similar observations were noted for Group C. Painful neuropathy was frequent (76%, 57%, 47% for Groups A, B, and C) with sensorimotor deterioration being the most common type. The yield of imaging studies was high with positive MRI reported in >70%. FDG-PET was performed in 40 patients (Groups A and B) and suggested the diagnosis in 84% and 90%, respectively. CSF cytology was positive in 40% across series and biopsy (76% patients) was confirmed in the diagnosis in 88%, 90%, and 80% in Groups A, B, and C, respectively.

O.68. EFFICACY OF TAILORED TREATMENT FOR HIGH- AND LOW-RISK MEDULLOBLASTOMA IN ADULTS: A LARGE PROSPECTIVE PHASE II TRIAL

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PURPOSE: To assess the efficacy of treatment of medulloblastoma (MB) in adults (>18 years). METHODS: Ninety-five MB patients were enrolled in a prospective phase II trial conducted between 1/2009 and 2/2009: 30 low-risk (LR) patients (T1, T2, T3a, M0, without postoperative residual disease) underwent radiotherapy (36 Gy) to the craniospinal axis, supplemented by a local tumor dose (18.8 Gy; total, 54.8 Gy), and 65 high-risk (HR) patients (T3b–T4, or postoperative residual tumor) received 2 cycles of “up-front chemotherapy” (cisplatin 25 mg/m2/day for 4 days, etoposide 40 mg/m2/daily for 4 days, and cyclophosphamide 1,000 mg/m2 on day 4; every 4 weeks) before the same radiation therapy, followed by maintenance chemotherapy if M1, M2, or M3 disease was present. RESULTS: Progression-free survival at 5 years (PFS-5) were 93% (100–86) in LR patients and 46% (23–70) in HR vs 50% (37–62) and 36% (23–49) in HR (P = .009 and P = .03, respectively) patients. Survival at 5 and 10 years (OS-5 and OS-10y) were 92% (81–100) and 65% (43–75) in LR vs 58% (46–71) and 43% (31–81) in HR (P = .002 and P = .02, respectively). Five-year and 10-year PFS was 68% (50–85) and 54% (34–74) in M0 patients vs 35% (18–51) and 19% (2–35) in M1–2–3 patients (P = .007 and P = .006). OS at 5 and 10 years were 71% (54–88) and 62% (43 81) in M0 vs 47% (29–65) and 26% (11–47) in M1–2–3 patients (P = .006 and P = .04); residual disease had no significant impact on 10-year PFS or 10-year OS. There were no deaths from toxicity, which was mainly hematological and successfully managed with dose reductions and supportive care. CONCLUSIONS: Since the incidence of MB in adults is extremely rare, data appearing in literature on this condition have been reported in small retrospective series. The findings made in the present prospective study on a large series of patients, the first of its type to appear in literature, clearly indicate the standard of care in MB in adults, and should constitute a benchmark for further studies.

O.69. PLASMA IGE LEVELS CORRELATE WITH THE DIAGNOSIS AND PROGNOSIS OF GLIOMA PATIENTS

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BACKGROUND: Previous studies have shown that glioma patients report allergies less frequently, and have lower IgE levels than controls. To evaluate its potential as a surrogate biomarker for glioma, we measured plasma IgE levels in 25 normal subjects and 232 glioma patients (85 grade II glioma patients, 40 grade III glioma patients, 70% of patients in this series were diagnosed during the last 8 years, and 72 patients (Group C) identified earlier during a 28-year period (1972–2000). Median age (55.5 years) and median number of anatomic structures affected (2) were similar among Groups A, B, and C. The predominant malignant cell type was B-cell, whereas T-cell-type tumor occurred in 10%, 23%, and 5% of Groups A, B, and C. In our series, NL affected more than 1 anatomic structure in 58% of patients with peripheral nerves, being the most frequently involved site (60%) while spinal, cranial nerve, and peripheral plexus infiltration occurred at a similar rate (40%–48%). Similar observations were noted for Group C. Painful neuropathy was frequent (76%, 57%, 47% for Groups A, B, and C) with sensorimotor deterioration being the most common type. The yield of imaging studies was high with positive MRI reported in >70%. FDG-PET was performed in 40 patients (Groups A and B) and suggested the diagnosis in 84% and 90%, respectively. CSF cytology was positive in 40% across series and biopsy (76% patients) confirmed the diagnosis in 88%, 90%, and 80% in Groups A, B, and C, respectively. In conclusion, NL is a challenging diagnosis but contemporary imaging techniques frequently detect the relevant neural involvement. Appropriate tailored therapy may prevent neurological deterioration and is associated with a prolonged survival in a subset of patients.
O.70. ANTI-ANGIOGENIC TREATMENT IN A CLINICALLY RELEVANT GliOBLASTOMA MODEL REDUCES BLOOD FLOW AND INCREASES TUMOR CELL INVASION
Centre de Recherche Public-Santé (CRP-Santé), Luxembourg, Luxembourg; University of Umeo, Umeo, Sweden; University of Bergen, Bergen, Norway

INTRODUCTION: Glioblastoma (GBM) is a highly vascularized tumor, and endothelial cell proliferation is one of the neuropathologic hallmarks of the disease. Therefore, the concept of interfering with the generation of new blood vessels has been attractive against tumors such as GBM. Recent studies have shown good response rates with bevacizumab, an antibody against vascular endothelial growth factor (VEGF). Yet, the effect is short lived and the physiologic mechanisms of bevacizumab action and the biologic consequences are poorly understood. MATERIAL AND METHODS: Here, we assessed the response to bevacizumab of highly angiogenic and invasive GBM xenografts, obtained by serial passaging of human GBM biopsies in nude rats. Animals with orthotopic tumors received weekly i.v. injections of 10 mg/kg bevacizu-

mab for 3 weeks. Before sacrifice, animals were analyzed by magnetic reson-
ance imaging to assess cellularity, and dynamic contrast enhancement MRI to assess tumor perfusion, and vascular permeability. After sacrifice, tumors were harvested for transcriptomic, proteomic, and metabolomic studies as well as histology and immunohistochemical analysis. RESULTS: In agreement with clinical data, we found that bevacizumab reduces vessel permeability and leakage of contrast agent in the brain barrier as reflected by the loss of contrast enhance-
ment and reduced Ktrans and Ve parameters. Interestingly, bevacizumab reduced blood flow and blood volumes, while spectroscopy data point at increased lactate concentration in treated tumors. A reduction in vessel number was observed while the extent of cell infiltration in the brain parenchy-

m was significantly increased. Key angiogenesis-related genes were upregul-
ated after treatment. CONCLUSION: Bevacizumab treatment in GBM leads to a reduction of blood vessels and increased tumor hypoxia which is accompanied by increased cell invasion. A novel model of tumor cell plasticity involving a metabolic switch will be discussed.

O.71. THE QUEST FOR HUD-SPECIFIC T CELLS: ATTEMPTS TO GENERATE A HUD-SPECIFIC T-CELL LINE
A. H. C. de Jongste, M. T. de Graaf, P. D. M. van den Broek, J. W. Gratama, and P. A. E. Sillevis Smitt – Daniel Den Hoed, Rotterdam, Netherlands

In the Hu paraneoplastic syndrome, a T-cell–mediated immune response targeted against the intracellular protein HuD is thought to be the cause of neurologic disease and neuronal destruction in patients with Hu disease expressing transcripts. However, HuD-specific T cells are rare, and extremely difficult to detect. Moreover, no HuD-specific T-cell lines are available to validate possible test strategies. Therefore, we tried to generate a HuD-specific T-cell line using two different approaches: (i) in vitro induction of HuD-specific T cells (ii) selection and expansion of HuD-specific T cells from peripheral blood of Hu–PNS patients. In the first experiment, peripheral blood mononuclear cells (PBMC) were drawn from 3 healthy CMV seronegative subjects and divided over 5 parallel cultures. Unloaded dendritic cells (DC), and DCs loaded with HuD protein, HuD peptide fragments mix (protein-spanning, overlapping 15mers), P665 protein, or P665 peptide mix were added to the subsequent cultures. Readout by intracytoplasmic IFN-γ production and addition of loaded DCs was performed at day 11, 21 and 31. In 3 of 3 subjects, a positive response to P665 peptide mix, and in 2 of 3 a positive response to P665 protein was found. However, none of the 3 patients showed a significant response to the HuD protein or HuD peptide mix. In the second experiment, PBMCs were drawn from 4 patients with a definitive diagnosis of Hu–PNS and used in 4 parallel cultures. These cells were stimulated with IL-2, and peptide-loaded autologous PBMCs were added every 2 weeks using the same peptides as in experiment 1, except P665 protein. Readout was performed every 2 weeks by flowcytometric intracellular IFN-γ and TNF-α staining. This regimen was continued 8–12 weeks. None of the 4 patients showed posi-
tive results to HuD protein or peptides. One of the patients was CMV seropo-
sitive, and indeed showed IFN-γ production upon stimulation with P665 mix. These experiments show that, although our methods were successful in the cases of EBV and EBV-related GBM, the described methods were not suitable in the context of an HuD-specific T-cell line, nor detection of HuD-specific T cells. Either the culture strategy does not stimulate HuD-specific T cells properly, or our readout method is not sensitive enough. Therefore, we recently started using an autologous feeder system, lowered the interval of adding stimulator cells to 1 week, and additionally performed readouts using flowcytometric CD107a and CD137 staining as markers for degranulation and T-cell activation. If successful, HuD-specific T cells would enable us to validate the methods used so far to detect HuD specific T-cell, and would offer an unique opportu-
nity to study HuD-specific T-cell function in vitro.

O.72. COMBINED USE OF MONOPOLAR AND BIPOLAR MOTOR MAPPING FINDINGS AND CORRELATION WITH DTI DATA DURING SURGICAL REMOVAL OF LESIONS INVOLVING MOTOR PATHWAYS
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Surgery of lesions involving motor areas or pathways requires their intra-
operative identification to guide resection and preserve functional integrity. The brain-mapping technique allows performing such an identification. DTI-FT reconstructs tracts, including CST, and SMA. This work reports the cor-

relation of intraoperative motor responses in all patients. The combined use of bipolar and monopolar DES failed to show fibers in the upper part of CST, whereas DES induced responses. In such cases, bipolar stimulation did not evoke responses, which were induced by monopolar stimulation. Monopolar stimulation evoked responses in 95% of patients, a high level of correlation was observed between DES and SMA findings. DTI-CST (3 DTI maps) was available in all patients, and in 40 also with different FA thresholds. DTI-CST and SMA was loaded onto the neuronaviga-
tion system and available intraoperatively for correlation with DES data. Motor responses were registered in all patients. They appeared as focal when CST was stimulated close to the surface, or affecting multiple muscles with deep stimu-
lation. The near-cortical stimulation induced overt movements, and deep cor-
tical stimulation induced muscle activations detected by EMG. In more than 95% of patients, a high level of correlation was observed between DES data and SMA findings. SMA techniques, bipolar and monopolar, evoked motor responses in all patients. The combined use of bipolar and monopolar DES and DTI-FT allowed to effectively and safely trace the tract.

POSTER PRESENTATIONS
[Poster numbers marked with * will also be presented orally in a Poster Session]

CELL BIOLOGY AND SIGNALING

P.001*. PROTEIN TYROSINE PHOSPHATASES IN GLIOMA BIOLOGY
A. C. Navin, J. W. J. Jeuken, J. T. G. Scheep, B. Celda, V. Esteve, W. P. Leenders, P. W. Wesseling, and W. J. A. J. Hendriks; 1Department of Pathology, Nijmegen Centre for Molecular Life Sciences, Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands; 2Department of Cell Biology, Nijmegen Centre for Molecular Life Sciences, Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands; 3Department of Physical Chemistry, University of Valencia, Valencia, Spain

Receptor tyrosine kinases (RTKs) such as EGFR, PDGFR, and MET are well known to have an important role in oncogenic signaling in gliomas. Phosphorylation of tyrosine residues on proteins through such RTKs can be counteracted by protein tyrosine phosphatases (PTPs). An important role for PTPs as “flip side of the coin” for RTK activity in glioma oncogenesis is therefore to be expected. Although the PTP PTEN is clearly functioning as a tumor suppressor in high-grade gliomas, the role of other PTPs is still largely unknown. To elucidate the relevance of PTPs in glioma biology, we first performed an in depth literature search that yielded information on 107 out of the 107 PTP genes present in the human genome to be potentially implicated in glioma biology. Besides PTEN, overexpression of PTPRZ is clearly associated with these tumors, although its exact function in oncogenesis is not clear at present. Also inactivating mutations, including
homoygous microdeletions, in PTPRD have been reported. Furthermore, some interesting PTPs that can counteract receptor tyrosine kinases, including TCFP (dephosphorylates EGFR), HSPK (crosstalk PTP/PI3K), and several PTPs that influence cell migration are on this list of PTPs that may regulate growth of glioma cells. To extend our knowledge on the role of PTPs in glioma biology, we performed expression profiling (Affymetrix U133 Plus 2 platform) and evaluated mRNA expression levels in glioma biopsies. RNA extracted from >70 glioma samples was hybridized to Affymetrix U133 Plus 2 arrays and data were imported in the dCHIP software program. Comparing different groups of glioma (eg, oligodendroglioma vs GBM, normal vs amplified EGFR), several PTPs were identified that displayed differential expression profiles. We further analyze the relevance of these candidates for glioma biology by exploiting overexpression and/or knockdown experiments in relevant orthotopic glioma xenograft models. Altogether, increasing evidence suggests that certain PTPs play a fundamental role in glioma biology. Interventions with such PTPs may complements the current therapeutic approaches and thereby contribute to the improvement of the prognosis for patients for these so far incurable tumors.

P.002*. DOWNREGULATION OF MEMBRANE PROTEIN UROKINASE-TYPE PLASMINOGEN ACTIVATOR RECEPTOR ASSOCIATED PROTEIN MAKES GLIOMA CELLS IMMOBILE AND CAN BE A TARGET FOR NOVEL GLIOMA THERAPY S. Takahashi, T. Kawase, and M. Toda; Keio University, Tokyo, Japan

The aim of this study was to identify a new target molecule that can be utilized for glioma anti-invasion therapy. In the present study, we have identified 4 candidate genes that express higher in glioma tissues compared with normal brain tissue by cDNA microarray analysis. Among the 4 genes identified, we focused on a membrane protein; urokinase-type plasminogen activator associated protein (uPARAP), which is one of the members of urokinase plasminogen activator system since previous reports discussed its relationship to cancer metastasis in breast cancer. uPARAP protein was expressed 4 of 4 (100%) glioma samples regardless of its World Health Organization grade, but did not express in normal brain control. Introduction of 2 independent small-interfering RNAs targeting uPARAP into 2 different glioma cell lines (KNS42 and KNS81) resulted in downregulation of uPARAP. Boyden chamber migration and invasion assay showed that downregulation of uPARAP decreases both invasiveness and migration property in vitro. Phalloidin staining showed that in uPARAP knocked-down glioma cells, polymeric actin became organized in stress fibers and the lamellipodia disappeared. On the basis of our findings, we suggest that RNA interference-mediated downregulation of uPARAP decreases invasion and migration property in glioma cells in vitro. The inhibition of invasion and migration property was mediated by the reorganization of the actin cytoskeleton. Downregulation of uPARAP could be a novel anti-invasion therapeutic strategy for malignant gliomas.

P.003*. METABOLIC CHARACTERIZATION OF STEM-LIKE Glioblastoma CELL LINES S. C. Dietz, N. Grifths, and C. Watts; 4Cambridge Research Institute, CRUK, Cambridge, UK; Centre for Brain Repair, Cambridge, UK

INTRODUCTION: The biology of glioblastoma multiforme (GBM) is poorly understood, but there is currently great interest in the metabolic make-up of this cancer type. METHODS: Cell lines derived from human GBM tissue were cultured under serum-free conditions following the Cambridge Protocol, which enriches the culture with tumor competent, self-renewing cells. We used 1H-NMR to analyze the concentrations of metabolites in cell extracts and cell media for 4 stem-like GBM cell lines. Since previous reports discussed its relationship to cancer metastasis in breast cancer, we performed expression profiling (Affymetrix U133 Plus 2 platform) and evaluated mRNA expression levels in glioma biopsies. RNA extracted from >70 glioma samples was hybridized to Affymetrix U133 Plus 2 arrays and data were imported in the dCHIP software program. Comparing different groups of glioma (eg, oligodendroglioma vs GBM, normal vs amplified EGFR), several PTPs were identified that displayed differential expression profiles. We further analyze the relevance of these candidates for glioma biology by exploiting overexpression and/or knockdown experiments in relevant orthotopic glioma xenograft models. Altogether, increasing evidence suggests that certain PTPs play a fundamental role in glioma biology. Interventions with such PTPs may complements the current therapeutic approaches and thereby contribute to the improvement of the prognosis for patients for these so far incurable tumors.

P.004*. REVERSAL OF EFFECT OF U87 DERIVED MICRO-VESELICS ON BIOLOGICAL PROCESSES OF Glioblastoma MULTIFORME M. L. Broekman, N. S. L. N. Maa, J. Skog, O. E. Breakefield, and M. Sana Estevas; 1Department of Neurosurgery, University Medical Center Utrecht, Utrecht, Netherlands; 2Neuro-oncology laboratory, Department of Neurosurgery, Erasmus Medical Center, Rotterdam, Netherlands; 3Department of Neurology and Gene Therapy, University of Massachusetts Medical School, Worcester, MA; 4Molecular Neurogenetics Unit, Department of Neurology, Massachusetts General Hospital, Charlestown, MA

Micro-vesicles, also known as exosomes, are extracellular, membrane-bound vesicles derived from the intraluminal membranes of multivesicular bodies (MVBs) of the endocytic pathway. These MVBs fuse with the plasma membrane, which causes the release of vesicles into the extracellular environment. Various cell types, including tumor cells, have been shown to produce micro-vesicles, which are believed to play a role in signal transduction. Recently, glioblastoma-derived micro-vesicles have been shown to contain proteins and RNA. Since micro-vesicles from different tumor cells appear to be involved in several biological processes, we set out to investigate the influence of U87 micro-vesicles on multiple biological processes, including angiogenesis and proliferation. After that, we treated U87 cells with interferon-β and isolated their micro-vesicles. These micro-vesicles were used to assess effects on the above-mentioned biological processes. We found that micro-vesicles derived from U87 cells but not from untreated, or treated with interferon-β cells, stimulate angiogenesis of glioblastoma cells. Micro-vesicles from both cells promote proliferation. Since we found that exosome production was unchanged, we studied the fusion capacity of these micro-vesicles as well as their protein and RNA content. Differences between the untreated and treated cells were observed. In conclusion, U87 micro-vesicles influence the behavior of glioblastoma cells. This can be reversed by treating the cells with interferon-β.

P.005*. TARGETING THE RELAPSE-INDUCING CELL POPULATION OF Glioblastoma M. S. Sena Esteves; 1Department of Neurosurgery, University Medical Center Utrecht, Utrecht, Netherlands; 2Neuro-oncology laboratory, Department of Neurosurgery, Erasmus Medical Center, Rotterdam, Netherlands; 3Department of Neurology, Bond, Germany; 4Institute of Reconstructive Neurobiology, Bond, Germany; 5Department of Surgery, Bond, Germany; 6Department of Pathology, Bond, Germany; 7Department of Radiation Oncology, Bond, Germany; 8Department of Neurosurgery, Bond, Germany; 9Department of Neuroscience, McKnight Brain Institute, Gainesville, FL

OBJECTIVE: Residual glioblastoma (GBM) cells that persist in the surrounding parenchyma after complete macroscopic resection represent one of the major driving forces of mortality in GBM. While exposed to postsurgical therapy, little is known on their biology. It was the goal of this study to isolate and profile these potentially relapse-inducing GBM residual cells. METHODS: Paired tissue specimens were obtained from 33 GBM patients. Residual GBM cells were derived from experimental biopsy of the resection margin after completion of standard neurosurgery. A second tissue sample, used as internal reference, was taken from the resected tumor core. Tumor cells were isolated, expanded under controlled in vitro conditions, and profiled (histology, growth kinetics, invasion studies, self-renewal analysis, qPCR, combined SNP/FISH analyses, FACs, in vitro drug–response assays, and xenotransplantation) in direct comparison. RESULTS: Sample analysis revealed residual cells as distinct malignant subentities in GBM. They fulfill the functional criteria of (rapidly proliferating, highly invasive) transit amplifiers rather than to represent (multipotent, self-renewing) stem cells. Stem-like GBM cells were almost exclusively detected in the routinely resected tumor core (71% of the center vs 14% of the periphery samples). Expression analysis revealed in 52 of 72 comparative measurements that mRNA levels of PDGFR-A/B, TGFβ-2, TGFR-1, VEGFR-2, FGF-1, FGF-2, and/or FGF-5 were elevated at and/or in the center of tumors. The expression of these markers is consistent among GBM tumors. The enrichment analysis related to overexpression of these genes revealed the enrichment of pathways related to angiogenesis and proliferation. After that, we treated U87 cells with interferon-β and isolated their micro-vesicles. These micro-vesicles were used to assess effects on the above-mentioned biological processes. We found that micro-vesicles derived from U87 cells but not from untreated, or treated with interferon-β cells, stimulate angiogenesis of glioblastoma cells. Micro-vesicles from both cells promote proliferation. Since we found that exosome production was unchanged, we studied the fusion capacity of these micro-vesicles as well as their protein and RNA content. Differences between the untreated and treated cells were observed. In conclusion, U87 micro-vesicles influence the behavior of glioblastoma cells. This can be reversed by treating the cells with interferon-β.
BACKGROUND: Multiple extracellular matrix proteins have been described to promote glioma cell motility accounting for infiltrative growth. Fibronectin (Fn) and vitronectin (Vn) have recently been targeted by cigenide (CTG), a cyclic peptide known to inhibit αvβ3 and αvβ5 integrins that interact with Vn (αvβ3/αvβ5) and Fn (αvβ3/αv5/3/5). Implemented in most glioma treatment modalities, radiotherapy is also shown to induce IGF-I receptor signaling. We recently demonstrated that photon irradiation enhances tumor cell migration at low doses, thus, possibly promoting tumor cell infiltration into the adjacent healthy brain. In the present study, we analyzed the effects of carbon ion irradiation on glioma cell migration ± the addition of CTG. METHODS: Twenty-four hours before migration experiments and FACS analyses, U87 glioma cells were irradiated with single photon doses of 1, 2, and 10 Gy using 6 MV photons at a linear accelerator. Particle radiotherapy was applied with an extended Bragg peak (E = 128 ± 7 MeV/μm, LET = (91.5 ± 1.5) keV/μm) at single carbon ion doses of 0.5 and 3 Gy at the Heidelberg Ion Therapy Center (HIT). The migration chambers were separated by 8-μm pore size polycarbonate membranes coated with Fn and Vn. Cells were preincubated with CTG well. After 24 h, cells that were stained and analyzed microscopically by an investigator blinded to experimental setup. Quantitative FACS analysis of integrin expression was performed with a BD FACSscan using PE- and FITC-labeled antibodies directed against αvβ3 and αvβ5, and expression of αvβ3/αvβ5 was not altered by CTG. In migration assays, CTG inhibited transmigration through Vn- and Fn-coated membranes. Photon irradiation increased migration on both Fn and Vn at low doses of 2 Gy. Addition of CTG to photon-irradiated cells decreased transmigration through Vn- and not Fn-coated membranes. FACS analyses revealed an increased expression of αvβ3 and αvβ5 following low-dose photon irradiation, which was still detected after single doses of 10 Gy. On the contrary, carbon ion irradiation alone significantly inhibited both Vn- and Fn-based transmigration and fully abrogated any migration if combined with CTG. Accordingly, expression of αvβ3 and αvβ5 was decreased following carbon ion doses of 0.5 and 3.0 Gy. CONCLUSION: Low doses of photons, such as applied in fractionated RT, bear the risk of promoting glioma cell migration on Vn and Fn. CTG may additionally be administered to counteract photon-induced hypermigration toward Vn; however, Fn-based migration is not affected by CTG. Carbon ion irradiation achieves strong inhibition of migration on both Vn and Fn, which is further increased by combination with CTG. Therefore, local infiltration of glioma cells may be prevented efficiently by using carbon ion RT in regimes combined with molecular targeted therapies.
might be crucial for glioma migration and possibly invasion. New panel of interactions between lactate metabolism and TGF-

Thus, we suppose LDH-A could influence the level of TGF-

leads to a decreased migration of high-grade glioma cells. DISCUSSION: THBS-1 leads to an increased level of activated TGF-

of LDH-A has been found in aerobic glycolysis, a mechanism well known
to influence the RNA and protein level of TSP-1 and consecutively the processing of

The dual lucerase assay was used for detection of AP-1 transcription factor activity.

RESULTS: Following transfection with KITENIN, the U251-KIT cell line exhibited decreased migration and invasion compared with the U251MG-E cell line. The U251-KIT cell line downregulated phosphorylated JNK and c-Jun, c-Src, and CAS. THBS-1 and THBS-2 in siLDH-A–

The final data analysis and the correlation between 14q32.31 LOH and other known prognostic markers, namely 1p, 19q, and 10q, and the methylation status of the promoters of MGMT and PTEN genes. METHODS: A microsatellite anaylsis was performed on DNA that was extracted from paraffin-embedded samples of 95 gliomas. LOH of 14q22.31 is evaluated by using D14S65 at 14q22.31 and D14h232 at 14q22.31 markers. The analysis includes 39 oligodendrogliotul tumors (54% WHO grade II) and 55 astrocytumours (52% WHO grade III and IV). The final data analysis and the correlation between 14q22.31 LOH and other markers will be presented at the conference.

Standard treatment of glioblastoma multiforme (GBM) consists of surgery, radiotherapy, and temozolomide (TMZ). Clinical data show that GBMs with wild-type methyl-guanine methyl-transferase (MGMT) gene, which express the MGMT DNA repair protein, are resistant to TMZ. The PI3K-Akt–

TGF-β2 activation by upregulation of THBS-1 leading to an enhanced migration of high-grade glioma in vitro. METHODS: We performed LDH-A knock-down by transfection of glioma cells with small interfering RNA directed against LDH-A (siLDH-A). Expression levels of TGF-β2 and THBS-1 in siLDH-A–

A microarray of LDH-A knocked-down glioma cell RNA showed downregulation of THBS-1 and TGF-β2. In this study, we tested the hypothesis that LDH-A influences TGF-β2 activation by upregulation of THBS-1 leading to an enhanced migration of high-grade glioma in vitro. METHODS: We performed LDH-A knock-down by transfection of glioma cells with small interfering RNA directed against LDH-A (siLDH-A). Expression levels of TGF-β2 and THBS-1 in siLDH-A–

LDH-A is a key metabolic enzyme catalyzing pyruvate into lactate and is excessively

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2 activation

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transfected cells were investigated using microarrays, RT-PCR, Western blot,

and by downregulation of the c-s src– and CAS-signaling pathways.

The dual lucerase assay showed that AP-1 transcription factor activity was also downregulated.

CONCLUSION: KITENIN inhibits migration and invasion of the U251MG human glioblastoma cell line by WNT/βCPC signaling cascades and through downregulation of the c-s src– and CAS-signaling pathways.

INTRODUCTION: Lactate dehydrogenase-type A (LDH-A) is a key metabolic enzyme catalyzing pyruvate into lactate and is excessively expressed in several human tumors. Transforming growth factor-β2 (TGF-β2) is a key regulator of invasion in high-grade gliomas, partially

remodeling the extracellular matrix (ECM) and inducing proteinases. Thrombospondin-1 (THBS-1) is an extracellular matrix protein important for activation and processing of TGF-β2. A microarray of LDH-A knocked-down glioma cell RNA showed downregulation of THBS-1 and TGF-β2. In this study, we tested the hypothesis that LDH-A influences TGF-β2 activation by upregulation of THBS-1 leading to an enhanced migration of high-grade glioma in vitro. METHODS: We performed LDH-A knock-down by transfection of glioma cells with small interfering RNA directed against LDH-A (siLDH-A). Expression levels of TGF-β2 and THBS-1 in siLDH-A–

transfected cells were investigated using microarrays, RT-PCR, Western blot,

and ELISA. Migration of transfected cells was investigated by Boyden Chamber and scratch assays. RESULTS: siLDH-A suppresses TGF-β2 in high-grade glioma and decreases the expression of THBS-1 on the RNA and protein level. THBS-1 leads to an increased level of activated TGF-β2 in supernatants of siLDH-A–treated cells. In migration assays, siLDH-A leads to a decreased migration of high-grade glioma cells. DISCUSSION: We demonstrate, for the first time, that knockdown of LDH-A can decrease the RNA and protein level of TSP-1 and consecutively the processing of TGF-β2. Additionally, knockdown of LDH-A decreases the RNA level of TGF-β2. Both results may contribute to an enhanced level of TGF-β2 and increased migration, given that LDH-A is expressed. An increased expression of LDH-A has been found in aerobic glycolysis, a mechanism well known from several human cancers. Recent paper showed that LDH-A is able to bind RNA. Thus, we suppose LDH-A could influence the level of TGF-β2 RNA by RNA stabilization. Together with our recent results that show that TGF-β enhances migration in high-grade gliomas, we demonstrate a new panel of interactions between lactate metabolism and TGF-β2 that might be crucial for glioma migration and possibly invasion.

Standard treatment of glioblastoma multiforme (GBM) consists of surgery, radiotherapy, and temozolomide (TMZ). Clinical data show that GBMs with wild-type methyl-guanine methyl-transferase (MGMT) gene, which express the MGMT DNA repair protein, are resistant to TMZ. The PI3K-Akt–

EGR-2–mediated activation of BAK expression is inhibited by the nuclear localization of upAR in glioma cell lines

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Glialoma progression is a highly complex process that involves the deregulation of proteins and genes that are responsible for tumor invasion, angiogenesis, circulation of tumor cells in blood vessels, colonization at secondary organ sites, and the tumor’s evasion of the host’s defense systems. The sPA/uPAR system has been postulated to play a central role in the mediation

P.010. ROLE OF KITENIN IN MIGRATION AND INVASION OF U251MG HUMAN MALIGNANT GLIOMA CELLS

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OBJECTIVE: KITENIN is a major molecule in the Wnt/planar cell polarity (PCP) pathway. The objective of this study was to determine whether and in which way KITENIN modulates the migration and invasion of a glioblastoma cell line. MATERIAL AND METHODS: In U251MG, one of the human glioblastoma cell lines, the expression of KITENIN was determined using Western blot. The difference in the migration and invasion abilities between the human glioblastoma cell line empty vector (U251MG-E) and KITENIN transfectants (U251-KIT) was evaluated using simple scratch test and matrigel invasion assays. Downstream signaling changes involving JNK, c-Jun, c-Src, and CAS were determined by Western blot. The dual lucerase assay was used for detection of AP-1 transcription factor activity.

RESULTS: Following transfection with KITENIN, the U251-KIT cell line exhibited decreased migration and invasion compared with the U251MG-E cell line. The U251-KIT cell line downregulated phosphorylated JNK and c-Jun, c-Src, and CAS. The dual lucerase assay showed that AP-1 transcription factor activity was also downregulated.

CONCLUSION: KITENIN inhibits migration and invasion of the U251MG human glioblastoma cell line by WNT/βCPC signaling cascades and through downregulation of the c-s src– and CAS-signaling pathways.

P.011. WARBURG EFFECT INFLUENCES MIGRATION OF HIGH-GRADE GLIOMA IN VITRO THROUGH ENHANCED TGF-β2 ACTIVATION BY THROMBOSPONDIN-1

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INTRODUCTION: Lactate dehydrogenase-type A (LDH-A) is a key metabolic enzyme catalyzing pyruvate into lactate and is excessively expressed in several human tumors. Transforming growth factor-β2 (TGF-β2) is a key regulator of invasion in high-grade gliomas, partially remodeling the extracellular matrix (ECM) and inducing proteinases. Thrombospondin-1 (THBS-1) is an extracellular matrix protein important for activation and processing of TGF-β2. A microarray of LDH-A knocked-down glioma cell RNA showed downregulation of THBS-1 and TGF-β2. In this study, we tested the hypothesis that LDH-A influences TGF-β2 activation by upregulation of THBS-1 leading to an enhanced migration of high-grade glioma in vitro. METHODS: We performed LDH-A knock-down by transfection of glioma cells with small interfering RNA directed against LDH-A (siLDH-A). Expression levels of TGF-β2 and THBS-1 in siLDH-A–

transfected cells were investigated using microarrays, RT-PCR, Western blot,

and ELISA. Migration of transfected cells was investigated by Boyden Chamber and scratch assays. RESULTS: siLDH-A suppresses TGF-β2 in high-grade glioma and decreases the expression of THBS-1 on the RNA and protein level. THBS-1 leads to an increased level of activated TGF-β2 in supernatants of siLDH-A–treated cells. In migration assays, siLDH-A leads to a decreased migration of high-grade glioma cells. DISCUSSION: We demonstrate, for the first time, that knockdown of LDH-A can decrease the RNA and protein level of TSP-1 and consecutively the processing of TGF-β2. Additionally, knockdown of LDH-A decreases the RNA level of TGF-β2. Both results may contribute to an enhanced level of TGF-β2 and increased migration, given that LDH-A is expressed. An increased expression of LDH-A has been found in aerobic glycolysis, a mechanism well known from several human cancers. Recent paper showed that LDH-A is able to bind RNA. Thus, we suppose LDH-A could influence the level of TGF-β2 RNA by RNA stabilization. Together with our recent results that show that TGF-β enhances migration in high-grade gliomas, we demonstrate a new panel of interactions between lactate metabolism and TGF-β2 that might be crucial for glioma migration and possibly invasion.
of these processes. We have demonstrated previously that the simultaneous downregulation of uPAR and uPA causes the activation of the extrinsic apoptotic pathway involving the mitochondrial ΔΨ collapse. From Western blot analysis of nuclear extracts from glioma cells (SNB19, U87) and xenografts (4910, 5310), we observed that uPAR is localized in the nucleus of these cells. Further analysis by immunoprecipitation, immunohistochemistry and transcription factor array revealed that uPAR was strongly associated with EGR-2 among other nuclear molecules. As determined by Western blot analysis of cytoplasmic extracts, RNAi-mediated downregulation of uPAR caused the activation of BAK expression and release of cytochrome c into the cytoplasm in SNB19, U87, and 4910 cells, and to a lesser extent, in 5310 cells. Downregulation of both uPAR and BAK retarded mitochondrial ΔΨ collapse from Mito-PT staining and Western blot analysis of cytochrome c release when compared with cells downregulated for uPAR alone. To determine whether uPAR binding to EGR-2 involved genetic material, we performed CHIP analysis by immunoprecipitating uPAR and PCR amplification of EGR-2–binding sequences. From the CHIP analysis, we observed that uPAR and EGR-2 form a complex with DNA in SNB19, U87, and 4910 cells, but form weak complexes in 5310 cells. Taken together, our results indicate the involvement of uPAR as a regulatory element with potential therapeutic implications.

P.015. ABERRANT HYPERMETHYLATION OF NON-PROMOTER ZYGOTE ARREST 1 (ZAR1) IN HUMAN BRAIN TUMORS
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Zygote arrest 1 (ZAR1) is a novel maternal-effect gene that plays crucial roles during the oocyte-to-embryo transition. Comprehensive methylation analysis of tumor-specific differentially methylated regions in human malignant melanoma has recently led to the identification of nonpromoter hypermethylation of the ZAR1 gene that has never before been linked to aberrant methylation. Importantly, ZAR1 hypermethylation was frequently observed in melanomas but was absent in benign nevi, and ZAR1 expression was found to be upregulated in melanomas. We searched for nonpromoter ZAR1 hypermethylation in 90 primary human brain tumor samples, normal brain tissue from 1 autopsy case, and 7 glioma cell lines, employing Sequenom MassARRAY, in which bisulfite-treated fragments are quantitatively detected by MALDI-TOF mass spectrometry. We also evaluated the ZAR1 transcript expression levels by quantitative real-time reverse transcription–PCR in 7 glioma cell lines. Hypermethylation of ZAR1 was frequently found in diffuse glioblastomas (7 of 7; 100%), anaplastic astrocytomas (16 of 17; 94%), glioblastomas (27 of 29; 93%), oligodendrogliomas (3 of 3; 100%), anaplastic oligodendrogliomas (3 of 3; 100%), and pituitary adenomas (9 of 10; 90%), but not at all in 3 pilocytic astrocytomas. Other tumor types showed infrequent ZAR1 hypermethylation: 1 (17%) of 6 of vestibular schwannomas and 4 (33%) of 12 meningothelial meningiomas. The normal brain tissue revealed no evidence of ZAR1 methylation. Among the 7 glioma cell lines, all cell lines displayed aberrant hypermethylation of ZAR1, while detectable ZAR1 transcript was not found in any of the cell lines. Our data indicate that nonpromoter hypermethylation of ZAR1 is extremely frequent in diffuse gliomas and pituitary adenomas, although methylation-related aberrant ZAR1 expression is less likely to be related to glioma tumorigenesis.

P.016. “ON-CALL” REFERRAL PATTERNS OF PATIENTS WITH BRAIN TUMORS IN TWO NEUROSURGICAL CENTERS: USING DATA TO ORGANIZE SERVICES
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BACKGROUND: In the UK, brain tumors account for up to 10% of all emergency referrals to a neurosurgical center and up to 6% of all out-of-hours emergency referrals. A better understanding of the patterns of referral could lead to an improvement in the organization and provision of services. METHODS: Data on all patients referred with suspected diagnosis of brain tumor to the “on-call” neurosurgical team in 2 units in the north east of England were collected over a 1-year period. Data included demographics, neurological status, and time of referral. These were analyzed using JMP 8.0.2. Categorical data were analyzed using the χ2 test and a two-tailed test was used to test for any association with significance level of 0.05. RESULTS: A total of 451 referrals were analyzed (mean age of patients was 60 years). Fifteen percent of referrals were received between 1700 and 0800 hours. Fifty percent of all “on-call” referrals were received between 1100 and 1700 hours with a peak at 1400 hours. Two percent of all referrals were received on a Friday. Up to 30% of brain tumor patients were referred from within the same hospital trust and increased significantly if the medical departments (which refer 60% of patients) were present on site (P < .05). Up to 27% of patients had focal neurological at the time of referral and 70% of patients had a Glasgow score of 14–15. Eighteen percent of all the emergency tumor referrals were admitted to the neurosurgical unit and only 3 patients were operated upon out-of-hours. CONCLUSIONS: The majority of referrals of patients with suspected brain tumors are received during normal working hours. Most are from medical departments in the catchment area and most patients have good neurological status. Streamlining referral pathways to the neuro-oncology multidisciplinary team during working hours will improve services for patients and reduce the workload of the on-call neurosurgeons.

P.017. WHO GRADE II GLIOMA DISTRIBUTION ON THE FRENCH TERRITORY: PRELIMINARY DETAILED RESULTS CONCERNING 6 REGIONS (ALSACE, BOURGOGNE, CHAMPAGNE/ARDENNES, FRANCHE, CONTE, LANGUEDOC-ROUSSILLON, AND LORRAINE)
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Diffuse infiltrating WHO grade II gliomas are relatively rare tumors. They account for 10%–15% of all gliomas with an incidence rate of 1 in 100,000 person-years, approximately. Epidemiological data are very rare and even exceptional. The aim of the present study was to estimate, with this preliminary work, the French national geographic distribution of all the histological cases of WHO grade II gliomas during a 4-year period. METHODS: The French neurosurgeons, neurologists, and neurooncologists, in collaboration with epidemiologists and biostatisticians, have established the French Brain Tumor Database (FBDTB) which is the biggest database concerning primary central nervous system tumors (PCNST) in Europe. This database continues to record all PCNST in France for which histological diagnosis is available. One of the major aims of this structure is to allow the realization of epidemiological studies. The methodology used for the geographic distribution analysis was simple: (i) identification of all the histological cases of glioma diagnosed between January 1, 2006 and December 31, 2009; (ii) for each glioma grade II, detection of the coexistence of the following address (postal code) of the patient at the moment of the surgical procedure; and (iii) description of the geographic distribution of all cases in the French territory with the search of spatial clusters. RESULTS: We analyze at present intraterritorial distribution of WHO grade II gliomas in 6 French regions (Alsace, Bourgogne, Champagne/Ardennes, Franche-Conté, Languedoc Roussillon, and Lorraine) corresponding to a population of 11 million of inhabitants. Preliminary results seem to show an important intraregional heterogeneity. The analysis at a national level is in progress. CONCLUSION: This original study aims to describe the geographic distribution of the WHO grade II gliomas at the level of the French territory. We will present the preliminary results concerning a population of approximately 11 millions of inhabitants.
EORTC-NCIC NCT0006353 randomized phase III trial (Snupp et al., NEJM) demonstrated significant improvements in survival yielding 16.0% long-term survivors. The present study aims to analyze to what extent these improvements within the setting of clinical trials translated to the population level. PATIENTS AND METHODS: A population-based survey on primary GBM cases, newly diagnosed in 2005, was conducted by the Austrian Brain Tumour Registry. The patient cohort was followed-up until December 12, 2008. A total of 375 adult primary GBM cases were identified; 75 (<18 years) were excluded. Survival analyses were performed according to Kaplan–Meier with two-sided log-rank tests. RESULTS: A total of 375 adult primary GBM cases were identified; referring to an age-standardized incidence rate of 4.3 in 100,000 person-years (95% CI 3.7–4.9) in males and 2.6 in 100,000 person-years (2.2–3.0) in females (WHO world standard population). Median age at diagnosis was 63.8 years, range: 18–87.0 years. Overall survival (OS) of the total cohort was 39.2% (34.3%–44.1%) at 1 year, 20.0% (16.1%–24.2%) at 2 years, and 15.5% (12.0%–19.3%) at 3 years. Significant differences in OS (P < .0001) were encountered between age groups 18–69 (n = 257, 68.5%) and 70+ (n = 118, 31.5%). Whereas in the age-group 18–69, the OS was 47.9% (41.6%–53.8%) at 1 year, 26.1% (20.9%–31.6%) at 2 years, and 19.8% (15.2%–24.9%) at 3 years, the respective rates of the age-group 70+ were 20.3% (13.6%–28.0%), 6.8% (3.2%–12.3%), and 5.9% (2.6%–11.2%). CONCLUSIONS: We show, for the first time, at the population level that GBM survival has increased when compared with historic data. The increase in survival is most prominent in the age group 18–69, whereas it is still poor in patients aged 70+. This favorable development at the population level seems to be because of innovations in diagnosis and therapy of brain tumors in the past decades, including the recent introduction of combined postoperative radiochemotherapy as new therapy standard in GBM.

P.019. NEOPLASTIC DIAGNOSIS TIMING PROFILE IN VON HIPPEL–LINDAU’S DISEASE: A PERSONAL SERIES EVALUATION
J. M. De Campos 1,2, M. Kusak 3, D. Aguirre 1, J. Montoya 4, J. Ayerbe 1, and J. L. Sarasa 1,2; 1Neurosurgery, Fundación Jiménez Díaz, Madrid, Spain; 2International, Madrid, Spain; 4Neuro-Radiology, Fundación Jiménez Díaz, inhabiting. The affected patients present nervous system and retinal hemangioblastomas (HGBs), associated among others with paragangliomas/pheochromocytomas (PGL), endolymphatic sac tumors (ELST), and renal cell carcinoma (RCC). The object of this study is to evaluate the present timing profile of these tumors in a series of affected patients. MATERIALS AND METHODS: Age and sequence of imaging confirmed diagnosis of intracranial HGBs, retinal HGBs, PGLs, ELSTs, RCCs, evaluated in a series of 54 affected patients with a total amount of 245 diagnosed tumors, from 30 families studied and followed in a neurological familial neoplastic syndrome referral center, based in a neurosurgical unit. The patient’s clinical data are compared within the obtained clinical groups. RESULTS: One hundred thirteen intracranial, 33 spinal, and 44 retinal HGBs were diagnosed. Retinal HGB diagnosis was more precocious, with initial diagnosis at 8 years of age, and a median at 28. Intracranial HGBs are first diagnosed at 8 with a median at 34 years of age. Spinal HGBs have a later diagnosis, beginning at 9 years of age, with a median at 37. PGLs diagnosis began at age 11, with a median diagnosis age of 33. ELSTs began at 23 years, with a median age of 37. RCC was the latest performed diagnosis, starting at 20 years with a median at 39 years. Three disease molecule–carried patient carriers have not developed tumors yet. Five patients have died as a result of their HGB, at age 30–60 years old, and 2 more from RCC, some later. No relation has been observed between age of presentation and other clinical or molecular characteristics (P > .05). CONCLUSIONS: In von Hippel–Lindau’s disease, the neoplastic occurrence begins at early age. Tumors are diagnosed in 20% of affected patients before age 19. A precocious diagnosis does not predict a more aggressive clinical course in relation to other clinical signs. On the other hand, the clinical temporal profile of the neoplastic disease cannot be predicted with the molecular diagnosis. Deaths before 60 in these patients are commonly related to hemangioblastoma. A molecular diagnosis should be provided to all first-degree relatives of affected patients at an early age, so that clinical and imaging studies can be performed by following patients, in order to obtain an early diagnosis and adequate management of these neoplasms.

P.020*. SUPPORTING PATIENTS WITH A DIAGNOSIS OF MALIGNANT GLIOMA: THE ROLE OF THE NEURO-ONCOLOGY NURSE SPECIALIST
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INTRODUCTION: In the UK, Guidance published by the National Institute for Clinical Excellence recommends for a “key worker” should be allocated to all patients with a diagnosis of intracranial tumor. It is a common practice that a neuro-oncology nurse specialist (NOSN) takes on this role and acts as a point of contact for patients, their carers, and all healthcare professionals involved in the patients’ management. Often the NOSN is a single-handed practitioner and data regarding their workload and involvement in patient care are scarce. OBJECTIVE: To assess the involvement of the NOSN in the management of patients with a diagnosis of high-grade malignant glioma. METHOD: Retrospective review of NOSN records relating to the management of all patients in our unit with a diagnosis of high-grade intracranial glioma (WHO Grades III and IV) during the period July 01, 2007 and June 30, 2009. NOSN involvement at key stages of the patient pathway together with liaison with patients, carers, and health professionals were assessed. RESULTS: A total of 123 eligible patients were identified (70 Males: 43 Females, mean age 59 years). Seventy-four percent patients had a diagnosis of glioblastoma. NOSN involvement at the time of initial consultation occurred in only 3% cases but rose to involvement in 93% cases during treatment. The NOSN had 705 contacts with patients and carers and dealt with 826 diverse issues, including clinic scheduling, symptom management, medication/steroids, psychological support, and referral to other agencies. Subsequently, the NOSN had 941 contacts with other health professionals (17 different agencies) to take forward patient care. CONCLUSION: The NOSN plays a key role in the management of patients with malignant glioma. This study indicates the high workload of the NOSN and their pivotal role in the management of this complex patient group.

P.021*. HEALTH-RELATED QUALITY OF LIFE IN PATIENTS WITH BRAIN TUMORS TREATED WITH TWO DIFFERENT TYPE OF FRACTIONATION
BACKGROUND: The aim of the study was to compare the quality-of-life (QOL) in patients with brain tumors treated with two different type of fractionation. MATERIALS AND METHODS: We measured the QOL in 78 patients with different type of brain tumors treated with postoperative radiotherapy with or without chemotherapy. The QOL was appreciated by using the QOL-C30 and QOL-BN20 questionnaires at the beginning and at the end of radiotherapy. There have been 27 women and 51 men with a median age of 53.5 years. The neurological index was 0 for 18 patients, 1 for 36 patients, 2 for 14, and 3 for 10 patients. They have been treated with conventional fractionation 1.8–2.0 Gy/fraction per day with a total dose of 54–60 Gy (53 patients) and with DT = 50–45 Gy with 3 Gy/fraction per day (25 patients). Conformal radiotherapy (3D) was applied in 60 patients. RESULTS: The acute toxicity at the end of radiotherapy was appreciated by using RTOG scale. This was 0 for 19, 23% of patients, 1 for 47, 44%, 2 for 32.05%, and 3 for 1.28% of patients. The health-related QOL coefficient was slightly better for all parameters at the end of radiotherapy, except nausea and vomiting (correlation coefficient r = .34). The correlation coefficient (r) was better for global health status (.95), physical functioning (.97), emotional functioning (.96), and cognitive function (.94). Motor dysfunction (.75), seizures (.78), and communication (.67) were altered at the end compared with the beginning of radiotherapy. The correlation between the type of fractionation (modified vs conventional) and QOL temporal profile is not predictable with the molecular diagnosis. Deaths before 60 in these patients are commonly related to hemangioblastoma. A molecular diagnosis should be provided to all first-degree relatives of affected patients at an early age, so that clinical and imaging studies can be performed by following patients, in order to obtain an early diagnosis and adequate management of these neoplasms.
P.024*. PRELIMINARY VALIDATION OF THE EORTC CHEMOTHERAPY-INDUCED PERIPHERAL NEUROPATHY QUALITY OF LIFE QUESTIONNAIRE (QLQ-CIPN20) SPANISH VERSION IN A SERIES OF MULTIPLE MYELOMA PATIENTS TREATED WITH BORT佐MEZOMB
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INTRODUCTION: Bortezomib-induced peripheral neuropathy (BIPN) presents in up to one-third of multiple myeloma (MM) patients treated with this drug before surgery (BTZ). The EORTC quality of life questionnaire, the QLQ-C30, has demonstrated to be reliable and valid when used with MM patients. The EORTC has developed the QLQ-CIPN20 questionnaire module to assess patients’ symptoms and functional limitations related to chemotherapy-induced peripheral neuropathy (PN). QLQ-CIPN20 consists of 20 items grouped into three scales assessing sensory, motor, and autonomic symptoms and functioning. The aim of the study was to determine the usefulness of the Spanish version of the QLQ-CIPN20 in a series of MM patients treated with BTZ. MATERIAL AND METHODS: A sample of 18 patients participating in a study evaluating the risk factors for developing BIPN (J. Periphr, Nerv Syst 2010;15:17–23) were asked to complete the QLQ-C30 and the QLQ-CIPN20 at baseline and during treatment. PN was graded according to the Total Neuropathy Score, both clinical (TNSc) and reduced (TNSr). QLQ-CIPN20 was compared at baseline between patients with and without PN, and at last visit between patients with and without BIPN. RESULTS: Prior to BTZ therapy, 6 patients had PN (5 had received vincristine previously). At baseline, patients with PN reported significantly more sensory (P < .01) and motor (P < .05) problems on the QLQ-CIPN20 than those without PN. Five of 18 patients developed BIPN. Patients with BIPN reported significantly more sensory problems than those without BIPN (P = .002) scale. No significant differences were observed on the final QLQ-CIPN20 in BIPN patients with or without prior PN at baseline. TNSc and TNSr baseline scores were significantly different between patients with and without PN (P = .001). Patients who developed BIPN showed differences in TNSc (P = .048) and TNSr (P = .048) in comparison with patients without BIPN. In the whole series, TNS was significantly correlated with QLQ-CIPN20 sensory (TNSc: r = .52, P < .001; TNSr: r = .57, P < .001), motor (TNSc: r = .37, P = .001; TNSr: r = .36, P < .002) and autonomic (TNSc and TNSr: r < .59, P < .001) scales. CONCLUSION: Our results confirm the usefulness of this questionnaire in detecting the impact related with sensory impairment in BIPN patients. Besides, QLQ-CIPN20 scales exhibit a significant correlation with TNS.

P.024*. THE LATE TOXICITY OF ADULT MEDULLOBLASTOMA TREATMENTS: THE EXPERIENCE OF 4 FRENCH CENTERS
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OBJECTIVES: Adult medulloblastoma is a rare tumor. Conventional treatment for the standard risk group (complete surgery or residual tumor lower than 1.5 cm3, absence of malignant cells in the cerebrospinal fluid, absence of metastasis, absence of MYC amplification and exclusion of large cells medulloblastoma) is classically based on a 54/36 Gy cranio-splanchnic radiotherapy (54 Gy on the posterior fossa and 36 Gy on the nevrraxis). Chemotherapy is proposed in complement for the high-risk group. This treatment is associated with an acute toxicity that decreases gradually when patient goes away from the treatment period. The French intergroup experience pleads also in favor of a late and progressive neurotoxicity for long survivors associated with a clear degradation of the quality of life. The purpose of this work was to compare changes we observed at baseline between the patient group and the controls in lexical diversity, repetition, self-corrections, and incomplete sentences. In the patient group, recent doctor’s visit, work, and hobbies were discussed. Within a sample of 300 words, speech from patients and controls is analyzed with regard to the following variables: lexical diversity (type token ratio), mean length of utterance (mlu), repetitions, self-corrections, and incomplete sentences. RESULTS: Statistical analyses revealed a significant difference (P < .01) between the patient group and the controls in lexical diversity, repetitions, self-corrections, and incomplete sentences. In the patient group, repetitions occurred most frequently, followed by self-corrections, and incomplete sentences. DISCUSSION: The results of this study suggest that a word finding deficit is the background of the distorted spontaneous speech of LGG patients. The availability of different words is restricted.

P.023*. COGNITION AND QUALITY OF LIFE IN PATIENTS WITH BRAIN TUMORS
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Damage to the brain areas involved in cognitive functions can have a crucial effect on the quality-of-life (Qol) of patients. Qol is an important topic that is increasingly relevant considering that gliomas typically affect young individuals potentially capable of returning to work. The objectives of this study were to develop a neuropsychological battery to investigate cognitive functions in patients with primary brain tumors, to identify any permanent cognitive deficit (in particular attention, language, and memory) and to study how patients after surgery perceive their functional status and social well-being. Two hundred patients with high- and low-grade gliomas in the right and left hemisphere were evaluated. We have developed an extensive neuropsychological battery that allow patient evaluation of patients and a selection of the patients suitable for awake surgery, while detecting the stimuli to use intraoperatively. Cognitive function (memory, language, attention, visuo-spatial orientation, and intelligence) was evaluated by means of this battery and a short interview was run to test their well-being perception. Patients were evaluated before surgery, immediately after surgery, and 3 months after surgery. This neuropsychological evaluation often revealed deficits in language competences or in memory abilities that hardly emerged from simple clinical evaluation. Patients immediately after surgery and follow-up had a high proportion of patients with a good recovery of cognitive functions and were able to carry out everyday activities.

P.023*. CHARACTERISTICS OF SPEONTANEOUS SPEECH IN PATIENTS WITH LOW-GRADE GLIOMAS IN ELOQUENT AREAS BEFORE SURGERY
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INTRODUCTION: Although it is already known that language deficits could occur in patients with LGGs, no previous studies are reported with respect to a detailed analysis of spontaneous speech. It must be noted that spontaneous speech is the most natural form of linguistic behavior. Patients with preoperative language disturbances are at-risk for more persistent aphasic disturbances; therefore, more insight into this subject is profitable. This study was conducted to investigate the spontaneous speech preoperatively in patients with LGGs in eloquent areas. METHOD: Thirty-four patients (22 males, 12 females) were included, and 21 healthy controls (8 males, 13 females) matched for age and education. Spontaneous speech from LGGs patients was collected for analysis and the complete surgical procedure and without tumoral progression (i), an analysis of the social status, (ii) an analysis of the quality-of-life status (HR EORTC QLQ 30 + Brain module), and (iii) an neuropsychological assessment. RESULTS: Thirty-four patients fulfilled the inclusion criteria. At this day, we collected social data in 15 cases, quality-of-life data in 14 cases, and a neuropsychological assessment in 19 cases. The work is still in progress and we will have supplementary data at our disposal for the meeting. The preliminary analysis shows that (i) only approximately 40% of the patients resumed a professional activity, (ii) the quality of life is altered, and (iii) despite the heterogeneity of the assessments, neuropsychological modifications seem mainly to concern attention and memory processes. CONCLUSION: As for the pediatric population, medulloblastoma adult survivors seem to present a late toxicity of the treatment. It justifies a discussion about the adaptation of the treatment modalities at least for the standard risk patients.
Repetitions could be a sign of time-gaining before the next content word. Self-corrections point to an earlier erroneously selected word. Sentences might be incomplete because of a lack of meaningful words. However, a syntactic component might be involved too. Our next step is to perform a fine-grained analysis of the spontaneous speech of LGG patients on the main linguistic levels: semantics, phonology, and syntax. Our goal is to select the sensitive parameters for improvement and deterioration of linguistic behavior in brain tumor patients pre- and postoperatively. A spontaneous speech analysis might be a more sensitive tool to detect language problems than structured language tasks, such as naming, all linguistic levels are involved.

P.026. CARING FOR A PATIENT WITH A MALIGNANT GLIOMA: AN ANALYSIS OF CARE-GIVER BURDEN
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BACKGROUND: The progressive physical and cognitive impairment experienced by patients with a malignant glioma (MG) places particular importance on the role of a patient’s primary caregiver. Providing care for a patient with MG can be particularly burdensome, impacting social, physical, and emotional quality of life (QOL). Given the importance of the caregiver in the course of treatment, the purpose of this study was to quantify and understand the responsibility of the caregiver experience. METHODS: Patients with MG within 6 months of initial diagnosis or relapse were eligible for this study if they had an involved caregiver. The Caregiver Quality of Life Index-Cancer (QOLC) was given to caregivers at baseline as part of a series of validated instruments to assess involvement and impact on them. The QOLC measures social, physical, and emotional strain on a caregiver through 35 items on 5-point Likert scales (0 = not at all to 4 = very much). The QOLC has a maximum score of 140 points, with a higher score reflecting better QOL. RESULTS: Completed QOLC questionnaires were collected from 22 caregivers to date. Of the 35 items, the 3 most strongly reported were increased levels of stress, distress over seeing their loved one deteriorate, and an increased fear of their loved one dying. The caregivers surveyed in this study scored an average of 80.6 on the 140-point scale. This is significantly lower (P = .01) than the average for caregivers across all cancers (93.3). We also found a significant difference between caregivers of patients with newly diagnosed vs recurrent MG. Caregivers of newly diagnosed patients were significantly more likely to feel sadness (P = .055) and feel that their life is imposed upon (P = .002), while caregivers of patients with recurrent MG were significantly more satisfied with their sex lives (P = .03). CONCLUSIONS: Results demonstrate the heavy burden placed on caregivers of patients with MG, particularly for those caring for newly diagnosed patients. This burden is likely to be greater than that experienced by caregivers of patients with other cancers; this may be related to the neurologic comprise of patients with MG. Caregivers play a crucial role in assisting MG patients; these findings demonstrate the negative impact on caregivers and the importance of the physician awareness so psychosocial interventions might be instituted.

P.027. HOW DOES TUMOR RESECTION AFFECT COGNITION? HIGH-GRADE GLIOMA VS MÉNINGIOMA PATIENTS
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INTRODUCTION: Many patients with intracranial tumors suffer from cognitive deficits. Because of differences in localization and growth speed, high-grade glioma (HGG) more readily damages healthy brain tissue compared with meningioma (MG). Surgical resection may diminish the pressure on the rest of the brain tissue, but it may cause additional harm neuronal tissue. Our aim is to compare the effects of tumor resection on cognition in patients with HGG and with MG. PATIENTS AND METHODS: Seventy-five patients (41 HGG, 34 MG) were tested preoperatively. Testing was repeated following surgery, and after subsequent therapy; the mean interval between the baseline test and baseline follow-up test was 8 (MG) weeks. Tumor size and site, use of anti-epileptic agents (AED), and the extent of resection were recorded. Validated neuropsychological tests for 8 domains were applied: general cognitive functioning (GCF), memory, working memory (WM), fluency, speed, perception, construction, and attention. RESULTS: Compared with normative data, preoperatively up to 50% of HGG patients and up to 28% of MG patients suffered from cognitive deficits. Mean preoperative test scores were lower in the HGG group than in the MG group, with significant differences in GCF, memory, and speed. In the HGG group, patients with large tumors tended to perform worse in fluency. Tumors located in the dominant hemisphere were related to significantly lower memory and WM scores. For MG patients, tumor size and site did not correlate with cognition. For both groups, no significant influence of AED on cognition was observed. Fifty-two patients (30 HGG, 22 MG) were tested post-surgery. Reasons for drop-out included refusal, post-surgical stroke, and progressive tumor growth. For HGG patients, mean postoperative test scores were improved compared with presurgical levels. The improvement was significant for construction and speed. Changes in performance after surgery were not related to the extent of resection. For MG patients, mean postoperative test scores declined (for perception, significantly), WM, and speed, while the other domains showed a nonsignificant increment compared with presurgery. All MG patients underwent a radical resection. DISCUSSION: HGG patients have more cognitive deficits than MG patients. Surgery leads to an improvement of cognitive functioning in HGG patients, while this effect is less clear in MG patients. This might be because of a shorter test interval in HGG, or because more severe cognitive deficits in HGG patients may more easily improve than the subtle deficits associated with MG.

P.028. A NEW ORIENTAL MEDICAL APPROACH TO ELIMINATE BRAIN EDEMA COMPROMISED WITH MALIGNANT BRAIN TUMORS: EFFICACY OF GOREISAN (AN AQUAPORIN INHIBITOR)
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OBJECTIVES: Glyceral, steroids, and isosorbide, which are covered by Japanese health insurance system, are widely used as medical decompression agents to eliminate brain edema complicated with malignant brain tumors and to relieve headache and several focal neurological deficits. Their side effects, however, sometimes prevent them from long-term use. For reducing brain edema, the authors have used the traditional oriental medical prescriptions for promoting diuresis and eliminating edema, such as goresian. Goreisan constitutes of 5 types of herbs-Polyporus g, Rhizoma Alismatis g, Rhizoma Alismatis g. The efficacy of Goreisan was investigated in 44 cases. The efficacy was evaluated with improvement rate of symptoms and neurological deficits: excellent (improvement rate > 50%), good (improvement rate 30% to 50%) or can significantly reduce the dose of glycerol and steroids), no effect, and deterioration. RESULTS: Excellent 18 (40.9%), good 30 (47.6%), and no effect 15 (23.8%). No significant complications were recognized. CONCLUSION: Goreisan can be used as a substitute for glycerol, isosorbide, and steroids to reduce mild brain edema.

P.029. STRENGTH OF SKELETAL MUSCLE IN GLIOBLASTOMA PATIENTS: AN ONGOING PILOT STUDY
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Glioblastoma (GBM) leads to a decrease in muscular strength as a result of neuromuscular dysfunction caused by GBM itself, and of corticosteroid medications which is needed to decrease intracranial pressure. Aim of this pilot observation was to test feasibility of strength testing in GBM patients. METHODS: Strength testing was so far performed in 2 patients (m:f = 4:1 patients), 54 ± 16a, BMI = 28 ± 4 kg/m2 at baseline and follow-up after 5 (± 2) months. One patient (Patient 5) dropped out because of death before follow-up; Patient 4 started with a training program after receiving the GBM diagnosis, the other patients reported no muscular training activity. Handgrip strength was measured by using a Jamar hand dynamometer. Isokinetic testing of both thighs (isokinetic knee extension and flexion strength) was performed by using a Biodex 3 dynamometer.
RESULTS: None of the patients showed side effects during or after the strength examinations. Handgrip strength of right hand/left hand measured for Patients 1–3: 16–62/10–44 (range) lb. Handgrip strength of (dominant) right hand increased in Patients 1, 2, and 4 (+9%–+10%), and decreased in patient 3 (−37%). Handgrip strength of left hand decreased in Patients 1–3 (−20% to −70%) (range), and increased in Patient 4 (+17%). Peak torques/weight (PT) of right knee extensors were in Patients 1–3: 91–290 (range) Nm/kg; PT of left knee extensors were 128–311 (range) Nm/kg. PT of right knee flexors were in Patients 1–5: 32–182 Nm/kg; PT of left knee flexors were 28–187 Nm/kg. At follow-up, isokinetic strength of knee extension and knee flexion decreased in 3 patients: extension of right knee (Patient 1 to 2, Patient 2 to 3, Patient 4 to 99%); flexion of right knee extended by 3%. Extension of left knee decreased in all 4 patients (Patient 1 to 5% to −51%). Flexion strength of both knees decreased in 3 patients (right knee: Patient 1–3: −16% to −59%; left knee: −22% to −32%). In Patient 4, isokinetic strength increased (+21%). CONCLUSION: Testing of muscular strength seems feasible in GBM patients. The results of this pilot observation indicate that strength of thigh muscles appears more than handgrip to decrease during the survival time. However, Patient 4 was able to increase his muscular strength through training.

P.012. COGNITIVE REHABILITATION IN NEURO-ONCOLOGICAL PATIENTS
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INTRODUCTION: Still now, despite therapeutic achievements of last decades in oncology, neuro-oncological patients are characterized by poor prognosis and low quality of life (Qol) during disease progression. Among neurological deficits, cognitive decline is one of the most common symptoms, with a severe impact on patients’ Qol. As pharmacologic interventions have not proven effective yet in the treatment of cognitive deficits, cognitive rehabilitation could represent an alternative approach. Literature research (Medline) evidenced 5 studies about this topic. Although all studies reported some successes, these are difficult to interpret because of limitations in the methods used. Additionally, both type and time of interventions, study population, and outcome measures were different, making studies not comparable. MATERIALS AND METHODS: Fifty-five patients (mean age 51 ± 14.4 years, range 25–79 years) affected by primary brain tumors referred to Palliative Home-Care Unit for Brain Tumor Patients, Regina Elena National Cancer Institute (Rome), from June to December 2009 were evaluated. All patients had already undergone surgery and chemotherapy and/or radiotherapy. All patients underwent a comprehensive neuropsychological examination assessing memory, language, attention, executive functions, and visuo-constructional skills. On the basis of literature review, we identified basic criteria for assessment of patients requiring cognitive rehabilitation program: (i) mild-to-moderate cognitive deficits (MMSE ≥18); (ii) life expectancy ≥ 6 months; (iii) KPS ≥ 70; (iv) age ≥18 years. Also we defined a standardized program consisting in: 1-hour-weekly individual sessions, lasting 10 weeks, carried out with a computer program. At now we enrolled 8 patients who are performing rehabilitation training. CONCLUSIONS: Limited data about cognitive rehabilitation in neuro-oncological patients has left many questions about the suitability of interventions in this population unanswered. Optimal timing, type, and intensity of interventions are unknown. Similarly, the role of factors such as tumor grade, prognosis, fatigue, disease duration, severity of cognitive impairment must still be clarified to establish eligibility criteria for cognitive intervention.

IMMUNOLOGY AND IMMUNOTHERAPY

P.033*. INTENSE HUMAN CYTOMEGALOVIRUS (HCMV) IMMUNE RESPONSE IN GliOBLASTOMA PATIENTS: A NOVEL PROGNOSTIC FACTOR FOR SURVIVAL
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BACKGROUND: Glioblastoma is a lethal malignant brain tumor with overall survival rates of <9.8% at 5 years. HCMV is a ubiquitous human herpesvirus found in nearly all humans worldwide with a persistent infection occurring in over 70% of adults. HCMV has been implicated in the development of several human malignancies owing to oncomodulatory effects of HCMV infection. It has been recently recognized that there exists an association between HCMV and malignant gliomas. Expression of HCMV nucleic acids and proteins has been described in >90% of gliomas in vivo. To study the prognostic value of anti-HCMV immune response in glioblastoma we prospectively assessed the levels of serum HCMV IgM and IgG in newly diagnosed glioblastoma patients and correlated the results with the clinical course. MATERIALS AND METHODS: Serum from 24 glioblastoma patients treated with standard chemo-radiotherapy in our institution between November 2008 and October 2009 were analyzed. Any HCMV IgM over 0.5 U/mL was considered diagnostic for acute HCMV infection. HCMV IgG >16 U/mL was regarded as positive for latent infection. Intense HCMV IgG immune response was defined as HCMV IgG >100 UI/mL. All clinical and pathological data were recorded in a database.
system using SPSS 13.0 statistics package. Response and progression-free survival time were defined, respectively, as objective response according to the 2D MacDonald criteria. Survival curves were generated using the Kaplan–Meier method and univariate analyses for survival differences were tested using two-sided log-rank tests. Cox’s proportional hazards regression model was used for multivariate analysis. RESULTS: After a median follow-up of 11.4 months, 13 patients (34%) have died. HCMV IgG was positive for latent infection in 9 patients (23%), 5 of whom had intense HCMV IgG immune response (20%). None of the patients had an acute HCMV infection. In univariate analysis, HCMV IgG >100UI/mL demonstrated a strong significant association with a longer overall survival \( P = 0.020 \). Positive HCMV IgG was found to be marginally associated with survival \( P = 0.07 \). In multivariate analysis, the only prognostic factors that retained statistical significance were complete tumor resection and age \( \geq 65 \) years. CONCLUSIONS: Intense HCMV IgG immune response is significantly associated with longer overall survival in our series. Further larger studies are required to validate HCMV IgG as prognostic factor for survival in glioblastoma patients.

P.034*. MODULATING THE IL-1 SIGNALING DURING GLIOMA ONCOTIC VIROTHERAPY

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There are no effective treatments for glioblastoma (GBM), and patients with this cancer have a life expectancy of 15 months from diagnosis. This poor prognosis is because of the difficulty in delivering appropriately targeted drugs to the brain and infiltrating margins of GBM. Thus, the capacity of oncolytic viruses (OVs) to generate progeny on-site that can spread throughout the tumor represents an ideal strategy for GBM treatment. However, the host innate immune response reduces OV replication in vivo and limits their therapeutic potential. It is therefore crucial to understand the mechanisms regulating anti-viral immunity to improve the OV efficacy. We have previously shown that intratumoral injection of OVs induces infiltration of phagocytes (macrophages and microglia) that inhibit viral replication and persistence. Pretreatment of animals with cyclophosphamide (CPA) depletes macrophages from the cancer area and OV spread and animal survival. However, the efficacy of the CPA + OV combined treatment is still poor. Indeed, more recent data indicated that macrophages are rapidly restored after CPA activity, leading to viral clearance, tumor re-growth, and animal death. Continuous systemic administration of CPA is toxic to the animals; therefore, it is important to find alternative means to prolong the immunosuppressive action of CPA in a more selective and less toxic fashion. We hypothesized that combination of CPA + OV armed with inhibitors of inflammation will prolong the immunosuppressive effects of CPA selectively in tumor tissue, thus resulting in enhancement of OV treatment while minimizing systemic toxicity. To test this hypothesis we have first identified the molecules that trigger OV-induced inflammation by analyzing tumor gene expression changes early after OV delivery. Our data showed 12 genes changing in expression; they were all induced by OV and belonged to the interleukin (IL)-1β signaling. Interestingly, IL-1β is an inflammatory cytokine with strong tumorigenic properties and the antagonist for IL-1 receptor (IL-1RA) is being tested for cancer treatment. We have then observed that IL-1β is induced in glioma cells by a combination of stromal factors and OV infection and inhibits viral replication in vitro. Systemic pretreatment of animals with IL-1RA prevents OV-induced intratumoral macrophage infiltration and increases OV spread. IL-1RA is a protein and does not cross the blood–brain barrier; thus, when delivered systemically, it did not inhibit activation of macrophage in response to intratumoral OV. We expect that CPA + OV armed with IL-1RA will result in a broad suppression of phagocytic cells and synergistic enhancement of oncolytic virotherapy. Altogether, we have identified the intratumoral signaling initiating OV-induced inflammation and these data can be used in a new strategy of virotherapy for GBM that presents strong potential for a synergistic treatment outcome.

P.035*. T-CELL BASED IDENTIFICATION OF TISSUE ANTIGENS BY AUTOMATED TWO-DIMENSIONAL PROTEIN FRACTIONATION

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BACKGROUND: Here, we describe a new method to comprehensively identify candidate tissue antigens that spontaneously cause T-cell responses in disease situations. MATERIALS AND METHODS: We used the new automated two-dimensional chromatography system PF2D to fractionate the proteome of tumor tissues and tested protein fractions for recognition by pre-existing tumor-specific CD4+ T-helper cells and cytotoxic T-cells. RESULTS: Applying this method to the ovalbumin (OVA) specific, TCRtg OT-I mouse model demonstrates efficient separation, processing, and cross-presentation to CD8+ T-cells by dendritic cells of OVA expressed by the OVA-transfected mouse lymphoma RMA-OVA. Applying this method to human tumor tissues, we identified in patients with head and neck cancer MUC-1 and EGFR as tumor-associated antigens selectively recognized by patients’ T-cells. Finally, we detected on an exemplary patient with a malignant brain tumor CD4+ and CD8+ T-cell responses against 2 novel antigens, transthyretin and calgranulin B, which were expressed on tumor and endothelial cells. Immunogenicity of these antigens could be confirmed in 4 out of 10 other brain tumor patients. CONCLUSIONS: This fast and cheap method appears suitable to identify candidate T-cell antigens in various disease situations, such as autoimmune and malignant diseases without restriction to their expression by a certain cell type or HLA allele.

P.036. HUMAN GLIOBLASTOMA CELLS DERIVED FROM NEUROSPHERES ARE MORE SENSITIVE TO NK, LECTIN-DEPENDENT, ANTIBODY-DEPENDENT, IL-1α-INDUCED NK CELL LYSIS AND IMMUNE-MODULATION OF T CELLS

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Glioblastoma multiforme (GBM) is a brain tumor with a very poor prognosis as a result of inevitable recurrence. During the past few years, a contingent of cells within tumors, so-called stem-like tumor cells (STC), has been characterized in GBM. These cells have similar properties to neural stem cells and can, with a limited number of cells injected in vivo in animals, reconstitute entire tumors. STC are also resistant to current radio- and chemo-therapeutic treatments in vitro. Therefore, STC are considered to play a key role in GBM recurrence observed in patients. These cells may be appealing targets for new therapeutic approaches such as immunotherapies. In this study, cells obtained from GBM specimen were grown in DMEM 10% FCS (adherent culture) and in serum-free medium supplemented with EGF and basic FGF (neurosphere culture). Phenotypic analyses confirm expression of stem cell markers such as CD133, nestin, and A2B5 on cells from neurospheres but not on cells from adherent cultures derived from cell lines derived from different GBM patients. Expression of HLA class I molecules is observed in cells from both neurospheres and adherent cultures. Regards tumor antigen expression, IL13Rα2 antigen is only observed on adherent cells. In contrast, EGF/VEGF is expressed at a higher level in cells from neurospheres than in cells from adherent cultures. Cell lines are then tested for their sensitivity to cell cytotoxicity mediated by NK and anti-tumor T cells. Human GBM cells grown as neurospheres are more sensitive to NK and CTL lysis compared with the same cells grown as adherent layers. Indeed, in contrast to their corresponding cells derived from adherent cultures, cells from neurospheres are sensitive to cell cytotoxicity mediated by resting NK cells or activated NK cells (with lectins, anti-CD28 antibodies, and IL-2). In addition, Melan-A—pulsed cells from neurospheres are sensitive to Melan-A—specific T cell lines, used as effectors, compared with cells derived from adherent cultures. In total, this study demonstrates that STC are suitable targets for immunotherapy using NK or specific T cells as effectors.

P.037. STUDIES OF NATURAL KILLER (NK) CELLS AGAINST GLIOMA INITIATING CELLS IN VITRO

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BACKGROUND AND OBJECTIVE: There is increasing evidence sustained the hypothesis that human gliomas originated from glioma-initiating cells or stem cells (GIC/GSC). And usually these cells could not be eradicated by conventional surgery, chemotherapy, and radiotherapy because of their stem-like properties. The cytotoxicity of natural killer (NK) cells against GIC in vitro was investigated. METHODS: The CD133+ glioma
cells were isolated from resected human glioblastoma specimens or glioma cell lines and were used as GIC. The NK cells were separated from peripheral blood mononuclear cells of glioma patients or healthy donors by Miltenyi magnetic beads, and were activated with IL2/PHA. Their in vitro cytotoxicity against GIC was assessed by lactate dehydrogenase (LDH) assay, with K562 cells as positive control target cells. RESULTS: The allogeneic NK cells could be cultured and activated with GIC-cultured medium, the increased cytolytic activity against GIC was shown with the higher E/T ratio. At the same E/T ratio, the activated NK cells showed remarkable higher cytolytic activity against GIC than that of resting (fresly isolated) NK cells (P < 0.01). CONCLUSIONS: The allogeneic NK cells could be activated in the GIC culture system and showed killing effect against GIC. It was suggested that activated NK cells might be used in the clinic for GIC eradication.

IN VITRO/IN VIVO MODELS

P.038*. ESTABLISHMENT OF TEMOZOLOSIDE-REFRACTORY GLIOMA CELLS
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PURPOSE: Temozolomide (TMZ) is an effective drug for the treatment of malignant gliomas; however, relapse of the tumor with the drug resistance development may be one of the major problems to be solved. Here, we established TMZ refractory glioma cell lines in vitro and analyzed their molecular characteristics including MGMT status. METHODS: To establish the TMZ-refractory glioma cell lines, human (U87, U251, U373, T98G, A172) and mouse glioma cell line (GL26) were repeatedly treated with TMZ at lower concentration (25 µM) and gradually at higher concentration (800 µM) every 4 days for about 2 months. MGMT expression of the cells was analyzed by Western blot. RESULTS: TMZ resistance developed in all the TMZ-sensitive cell lines without MGMT expression (U87, U251, U373, A172, and GL26) except in TMZ-resistant T98G cells with MGMT expression and mutant type p53. The degree of resistance to TMZ appeared about 2–3-fold higher than that of normal glioma cell lines. No difference was found in MGMT expression level between TMZ refractory cells and normal cells. The drug resistance and MGMT expression were not affected by the cell passage number. CONCLUSION: The newly established cell lines would be useful in the development of in vitro and in vivo TMZ-resistance experimental model.

P.039*. HIGH-RESOLUTION NMR SPECTROSCOPY OF BRAIN-DERIVED STEM CELLS
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NMR spectroscopy of living organisms provides a noninvasive and comprehensive insight into cellular composition and metabolism. In addition, identifying cell-specific NMR spectroscopic signals and patterns may lead to in vivo detection and tracking of different cell types including stem cells. We established high-resolution 1H NMR spectroscopy of several cultured human-derived stem/progenitor cell lines like Notin-positive fetal murine neural progenitors (NPCs), DCX-positive adult murine neuroblasts, and CD13+ human glioblastoma-derived cancer stem cells (CSCs), all cultured under serum-free conditions. Measurements are performed at Bruker Avance 600 MHz (14.1 T) and 800 MHz (18.8 T) spectrometers equipped with TCI cryo probes. Employing a metabolomic approach including spectroscopic filtering techniques, sophisticated quantification methods, and correlation analysis of spectroscopic and biological data, we investigate both metabolites and NMR-visible macromolecules (ie, so-called mobile lipids and mobile proteins, regarding their stem cell specificity and their response to targeted modulation of proliferation and differentiation, for example, by means of transforming growth factor β [TGF β]). Subsequently, high-resolution NMR spectroscopy of cultured brain-derived stem cells may contribute to the key link between the fundamentals of stem cell identification and metabolism on the one hand, and on the other hand the possibility of monitoring neurogenesis, neurodegenerative diseases, and tumors regarding both diagnosis and therapy noninvasively in vivo in humans.

PREDICTIVE BIOMOLECULAR MARKERS

P.040*. SCREENING CHEMOTHERAPY AGENTS USING SURGICALLY OBTAINED BRAIN TUMOR SPECIMENS
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BACKGROUND: Surgical brain tumor specimens can be used to obtain valuable information regarding sensitivity to drug therapies. Data collected on surgical specimens using an in vitro growth and invasion assay were correlated with patient response to chemotherapy. METHODS: Surgically obtained glioma tumor specimens were cultured in a 3-dimensional collagen gel matrix and observed for growth and invasion. Chemotherapy drug effects on mean invasion and growth were expressed as a ratio relative to control conditions. Temozolomide (TMZ) sensitivity was correlated with methyl-guanine-methyl transferase (MGMT) methylation status. Length of patient survival was compared between TMZ-treated patients whose screening results had predicted a positive response and those predicted to have a negative response. RESULTS: Tumors from individual patients differed in terms of response profiles, especially when response was defined as at least an 80% reduction in tumor invasion distance. Similarly, different drugs varied in their ability to inhibit tumor growth and invasion, with only 9 of 31 (29%) tumors responding to TMZ, compared with 100%, 94%, and 90% response rates for paclitaxel, cis-platinum, and vincristine, respectively. Length of survival in TMZ-treated patients who screened positive for a TMZ response averaged 301 days, vs just 98 days in their TMZ-negative counterparts. CONCLUSIONS: In this study, we report a novel assay system that generates individual patient drug profiles, and an ability to predict patient survival in TMZ-treated patients. Further research, including a formal prospective clinical trial, may be warranted.

P.041*. STROMAL-DERIVED FACTOR 1A (SDF-1A), A HOMING FACTOR FOR MENENCHYMAL PROGENITOR CELLS, IS ELEVATED IN TUMOR TISSUE AND PLASMA OF GLIOMA PATIENTS
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Malignant gliomas are a fatal disease without sufficient possibilities for early diagnosis and a lack of chemical markers to detect remission or relapse. The recruitment of progenitor cells like mesenchymal stem cells (MSC) is a main feature of gliomas. SDF-1, a chemokine produced in glioma cell lines, enhances migration in MSC and was associated with cell survival and apoptosis in gliomas. Therefore, this study was performed to evaluate (i) whether SDF-1 and its receptors are expressed in human malignant glioma in situ and (ii) if SDF-1 might potentially play a role in recruiting MSCs into human glioma. In glioblastoma tissue, immunohistochemistry revealed that SDF-1 and its receptor CXCR4 are expressed in regions of angiogenesis and necrosis, qPCR showed that SDF-1 is elevated and public expression data indicate that CXCR4 is upregulated. The latter data also illustrate that SDF-1 could be up- or downregulated in glioma compared with normal brain in a transcript-specific manner. In plasma, SDF-1 is elevated in glioma patients. The level is reduced by bexaemethaione intake and surgery. Dexamethasone also decreased SDF-1 production in the cells in vitro. Undirected migration of hMSC was not enhanced by addition of SDF-1. However, SDF-1 stimulates directed invasion of hMSC in a dose-dependent manner. Taken together, we show that SDF-1, a potent chemotactrant of progenitor cells like hMSCs and its expression is elevated in glioma tissue, resulting in elevated SDF-1 levels in the patient’s plasma samples with concomitant decrease after tumor resection. The fact that elevated SDF-1 plasma levels are significantly decreased after tumor surgery could be a first hint that SDF-1 might act as tumor marker for malignant gliomas to detect disease progression or remission, respectively.
P.042. CYTOPLASMIC SUBLOCALIZATION OF THE STEM CELL-ASSOCIATED PROTEIN ASPM IS AN INDEPENDENT PROGNOSTIC FACTOR IN ASTROCYTIC GLIOMAS

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OBJECTIVE: Recently, tumor initiation, tumor recurrence, and therapy resistance in astrocytic gliomas have been attributed to the existence of brain tumor stem-like cells. ASPM (abnormal spindle-like, microcephaly associated), a stem-cell-associated protein, is a key regulator of the symmetric division of self-renewing stem cells that controls spindle orientation during cell division and therefore localizes to the cytoplasmic centromeres during interphase (cASPM) and around the nucleus during mitosis (nASPM). In this study, we correlated its expression in a tissue microarray (TMA) comprising samples of 334 gliomas to WHO grade, the proliferation marker Ki-67, and patient outcome. METHODS: Formalin-fixed, paraffin-embedded tissue samples of 283 primary astrocytic gliomas WHO II–IV and 51 recurrences were used for TMA design. Detection of primary antibodies directed against ASPM, Ki-67, and the appropriate secondary antibodies was carried out with Vectastain ELITE ABC Kit. Staining was graded semiquantitatively from 0 to 5 according to the percentage of positive cells covering the whole tissue spot. Cytoplasmic and perinuclear staining was analyzed independently. The relationship between ASPM expression, WHO grade, and Ki-67 was quantified using Spearman’s rank correlation coefficient. To exclude potential confounders of survival, WHO grade, age at diagnosis, and extent of resection were included in a multivariate Cox proportional hazards regression. RESULTS: Perinuclear expression of ASPM was neither associated with WHO grade nor with patient outcome. Cytoplasmic expression of ASPM, however, resulted in a significant prolongation of overall survival (OS) both in gliomas of all WHO grades (P = .021) and in the subgroup of glioblastomas (P = .026) as well as to malignant progression (P = .026) in gliomas WHO II–IV, independent of known prognostic confounders. Even though no significant correlation between WHO grade and cASPM expression was found, there was a trend towards a decreased expression both in case of malignant progression and recurrent glioblastoma. Importantly, a significant inverse correlation between cASPM and Ki-67 was found both in tumors of all WHO grades (P < .0001) and in glioblastomas (P = .0002). CONCLUSION: Our study indicates that overexpression of cytoplasmic ASPM in astrocytic gliomas WHO II–IV is a strong prognostic indicator in favor of a favorable patient outcome and is associated with a more aggressive phenotype in terms of proliferative capacity and tumor recurrence.

P.043. EPO AND EPOR IN HUMAN Glioblastoma: FRIEND or FOE?

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INTRODUCTION: Erythropoietin (Epo) is a well-known factor of erythropoiesis and is therefore used to treat anemia in neoplastic disease. In addition, Epo exerts neuroprotective effects via Epo-receptor (EpoR) on neuronal cells. This makes a prophylactic use against neurocognitive impairment caused by radiochemotherapy probable. Epo-EpoR signaling, however, has also been recognized in various tumors such as glioblastomas. Several studies during the last years performed in vitro and in vivo reported conflicting results on the effect of Epo on malignant gliomas. We analyzed here the impact of Epo and EpoR expression on the prognosis of human glioblastomas in different treatment groups. METHODS: We established retrospectively a bank of human glioblastomas with complete documentation of clinical course and treatment. The expression of Epo (n = 64) and EpoR (n = 66) was assessed by immunohistochemistry and analyzed with semiquantitative scores. The results were assessed separately for short- or long-term survival in the treatment groups by univariate and multivariate analysis with respect to age, gender, chemotherapy, and extent of resection. RESULTS: High expression levels of EpoR were correlated with a median survival advantage of 8 months (P < .01) in patients under 60 years of age. High levels of both Epo and EpoR were associated with a significant prolongation of median survival when compared with low levels of both molecules. In patients treated with radiochemotherapy adjuvant to operation, a trend to 6-month longer median survival was observed in association with high levels of EpoR expression that just failed significance (P = .06). By multivariate analysis, a positive correlation of EpoR (P = .02) with longer patient survival proved to be significant. DISCUSSION: In accordance with some of the previous studies, we found evidence for a longer patient survival associated with higher expression levels of EpoR in human glioblastomas. A therapeutic use of Epo for anemia in glioblastoma patients seems therefore to be safe with respect to tumor growth. A prophylactic use (ie, for neuroprotection, however) cannot be recommended in light of the functional studies described in the literature.

P.044. METHYLPHENIC SENSITIVE HIGH-RESOLUTION MELTING ANALYSIS: QUANTITATIVE ASSESSMENT OF MGMT PROMOTER METHYLATION IN HIGH-GRADE GliOMAS

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The methylation status of the MGMT (O6-methylguanine-DNA methyltransferase) gene has been shown to be a predictive marker in high-grade gliomas treated with temozolomide. Methylation-specific PCR (MSP) is widely used for the detection of the MGMT methylation. Despite its widespread use, MSP has several disadvantages. False positives may occur if primers are badly designed or used at too low a temperature. Moreover, MSP is not quantitative, but simply dichotomous. To exclude potential confounders of survival, WHO grade, age, and extent of resection were included in a multivariate Cox proportional hazards regression. RESULTS: Perinuclear expression of ASPM was neither associated with WHO grade nor with patient outcome. Cytoplasmic expression of ASPM, however, resulted in a significant prolongation of overall survival (OS) both in gliomas of all WHO grades (P = .021) and in the subgroup of glioblastomas (P = .026) as well as to malignant progression (P = .026) in gliomas WHO II–IV, independent of known prognostic confounders. Even though no significant correlation between WHO grade and cASPM expression was found, there was a trend towards a decreased expression both in case of malignant progression and recurrent glioblastoma. Importantly, a significant inverse correlation between cASPM and Ki-67 was found both in tumors of all WHO grades (P < .0001) and in glioblastomas (P = .0002). CONCLUSION: Our study indicates that overexpression of cytoplasmic ASPM in astrocytic gliomas WHO II–IV is a strong prognostic indicator in favor of a favorable patient outcome and is associated with a more aggressive phenotype in terms of proliferative capacity and tumor recurrence.

P.045. THE PROGNOSTIC/PREDICTIVE ROLE OF IDH1 GENE MUTATIONS IN PATIENTS TREATED WITH RECURRENT GLIOBLASTOMA

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BACKGROUND: Somatic mutations in the isocitrate dehydrogenase 1 (IDH1) gene have been frequently found in low-grade glioma (WHO grade II–III), less frequently in secondary glioblastoma (sGB), and are rare in de novo glioblastoma (dGB), and associated with a significantly younger age and a better survival from primary diagnosis. The aim of this study was to investigate the correlation between IDH1 gene mutation status and clinical outcome in patients with recurrent glioma enrolled in phase II trials with the EGFR-targeted monoclonal antibody cetuximab and the VEGFR inhibiting small molecule sunitinib. METHODS: Somatic DNA was extracted from formalin-fixed and paraffin-embedded tumor tissues of 52 patients with recurrent glioma, 36 of which were treated with cetuximab, and 16 who were treated with sunitinib in the context of two prospective phase II clinical trials. Nested PCR and denaturing gradient gel electrophoresis (DGGE) were performed to detect IDH1 mutations; codon 132 of IDH1 was sequenced in case of an abnormal DGGE pattern. RESULTS: IDH1 mutations (G395A in 15 cases and C394T in 1 case) were found in 8 of 14 (57%) grade II–III glioma, 4 of 7 (57%) sGB, and 4 of 10 (40%) dGB (P < .05), and were associated with a younger age (P < .05). Patients with IDH1 mutations had a longer progression-free survival (PFS) and overall survival (OS) from initial diagnosis (P < .05 for both). IDH1 mutation status was not significantly correlated with TTP or OS from the time of recurrence in the sunitinib and cetuximab studies. A trend (P = .07) was observed for IDH1
wild-type patients to have a superior survival in the cetuximab-treated cohort but not in the sunsitumib cohort. CONCLUSIONS: We confirm in this study, population that mutation of the IDH1-gene is correlated with the WHO differentiation grade and survival from initial diagnosis. IDH1 mutation status does, however, not correlate with survival from the time of recruitment in these two studies on recurrent glioma. A negative correlation with OS may be present in patients treated with the anti-EGFR-targeted mAb cetuximab. Further study is currently ongoing in one-third cohort of patients treated with bevacizumab at the time of recurrence. Updated results will be presented at the meeting.

P.046. IDH1 AND IDH2 MUTATIONS AND THEIR CORRELATIONS IN GLIOMAS

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INTRODUCTION: Somatic mutations of isocitrate dehydrogenase enzyme isozymes 1 (IDH1) and 2 (IDH2) have been recently described in a high percentage of primary gliomas and oligodendrogliomas. The two isozymes catalyze the conversion of isocitrate to α-ketoglutarate with reduction of NADP+. Mutations are preferentially located in exon 4 of both IDH1 and IDH2 genes, affecting arginine at codon 132 (R132) of IDH1 gene and the codon 172 (R172) of IDH2 gene. MATERIALS AND METHODS: Search for mutations in IDH1 and IDH2 genes was investigated in a series of 120 grade IV (glioblastomas), 32 grade III (10 astrocytomas and 22 oligodendroglias), and 44 grade I–II gliomas (10 pilocytic astrocytomas, 10 diffuse astrocytomas, and 24 oligodendroglias). Analysis was performed on formalin-fixed and paraffin-embedded surgical samples by direct sequencing. RESULTS: Distribution of IDH1 mutations was inversely correlated with histological grade, occurring in 50% of diffuse astrocytomas grade II, 10% of pilocytic astrocytomas, 75% of oligodendroglias grade II, 36% of oligodendroglias grade III, and 2% of tumors grade IV. The majority of mutations were in IDH1 gene: R132H accounting for 91% of cases, R132Q for 6% and R132C for 3%. Those of IDH2 gene (R172K) were limited to 1 glioblastoma and to 1 oligodendroglioma. Associations of IDH1 mutations were tested for the following molecular markers: MGMT hypermethylation, LOH of 1p/19q, EGFR amplification, and TP53 mutations. IDH1 mutations showed a trend towards a positive association with MGMT hypermethylation and LOH of 1p/19q, whereas they were mutually exclusive with EGFR amplification (P = 0.0346). CONCLUSIONS: IDH1 and IDH2 mutations may represent an early genetic event in gliomagenesis, preceding the differentiation of precursors, and may be considered prognostic. It is conceivable that they are preserved in secondary glioblastomas. The latter must be rather rare in our collection where none of the glioblastomas was diagnosed at a second surgery after a previous astrocytoma.

P.047. SERUM S-100B PROTEIN IS A PREDICTOR OF SURVIVAL IN RECURRENT GLIOMA

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BACKGROUND: S-100B protein is raised in serum after cerebral damage and disruption of the blood–brain barrier. In a pilot study, high serum levels S-100B in glioma patients were associated with shorter survival. Our aim was to evaluate the value of S-100B in serum as a prognostic marker in treatment of malignant glioma as a response to chemotherapy. PATIENTS AND METHODS: Serial samples of 22 patients with recurrent glioma were obtained before, during, and after chemotherapy. Serum S-100B was measured and a Kaplan–Meier curve was drawn for high and low serum concentrations (cut off value of 0.1 μg/L). RESULTS: Recurrent glioma patients with a high serum concentration S-100B at baseline had a significantly shorter survival compared with patients with a low concentration (P = 0.000). No trends were detectable in serial measurements. No correlation was found between S-100B concentration and age, gender, tumor pathology, or response to chemotherapy. CONCLUSION: In patients with recurrent glioma, serum concentration S-100B is a strong predictor for survival.

P.048. TEMOZOLAMIDE AND RADIOTHERAPY IN NEWLY DIAGNOSED GLOBLASTOMA PATIENTS: MGMT PROMOTER METHYLATION STATUS AND Ki-67 AS BIOMARKERS FOR SURVIVAL AND RESPONSE TO TREATMENT

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AIMS: This phase II study aims at investigating the correlation between 5-α-methylguanine DNA-methyl transferase (MGMT) promoter methylation status with Ki-67-labeling index, and responsiveness to radiation therapy (RT), and overall survival (OS) in newly diagnosed patients with glioblastoma (GBM) who are treated with temozolomide (TMZ) concomitant with and adjuvant to radiotherapy (RT). PATIENTS AND METHODS: From June 2005 to [Unsupported Character--&#161;]8161] June 2008, 34 patients with newly diagnosed GBM received TMZ 75 mg/m² as radiosensitizer plus RT 2 Gy/ treatment up to 60 Gy, followed by TMZ 175 mg/m² for 5 days every 4 weeks for 12 doses. Methylation-specific PCR assay and Ki-67 expression were performed on the tissue blocks. The patients were followed by MRI while MR spectroscopy (MRS) was performed to confirm progression and according bevacizumab 10 mg/kg every 2 weeks was added to 7 patients till further progression was proved. RESULTS: Three patients were omitted because of lack of tissue specimens, else, 12 specimens with complete response (CR), 14 had partial response (PR), and 7 had stable disease (SD), while 8 patients (25.8%) had progressive disease (PD). The ODC was significantly higher among methylated patients and in those with Ki-67 >17% (P = 0.003). The median overall TTP was 12 months and the median OS was 20 months, the methylated patients had a higher median TTP of 13 months (range 8–18 months, CI 95% of 9.36–12.9), and OS of 24 months (range 12–31 months, CI 95% of 16.1–21.3), while the unmethylated patients had a median TTP of 6.5 months and a median OS of 12 months which was highly significant (P = 0.0001).

Patients with Ki-67 <17% had a median TTP of 16 months and median OS of 24 months compared with 7 and 12.5 months, respectively, for the patients with Ki-67 ≥17%. The multivariate analysis of both methylation status and Ki-67 showed a nonsignificant correlation to ODC, TTP, and OS. Significant correlation was found between the ODC, TTP, and OS with age <52 years (P = 0.001), tumor excision vs biopsy (P = 0.0001), and the number of TMZ doses received ≥10 doses (P = 0.002). The common G3 and G4 toxicities were lymphopenia and neutropenia in 3 patients (9.67%), thrombocytopenia in 4 patients (12.9%), and 1 patient with G3 constipations (3%), all were medically manageable. CONCLUSION: This study showed that MGMT promoter methylation status and the Ki-67 status could serve as independent predictive and prognostic markers of response and survival, they also might identify a group of patients who could benefit from combining further therapeutic agents to the TMZ.

P.049. EVALUATION OF IMMATURE AND ABSOLUTE PLATELET COUNT CHANGES AS PREDICTORS OF SEVERE THROMBOCYTOPENIA IN MALIGNANT GLIOMA PATIENTS TREATED WITH TEMOZOLOMIDE

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BACKGROUND: Temozolomide (TMZ) is commonly used for therapy of malignant glioma and induces severe thrombocytopenia in a small fraction of patients. Currently, no biomarkers predicting TMZ-induced thrombocytopenia are available. In this study, we investigated whether changes in platelet count (PLT) or the immature platelet ratio (IPF) may serve as predictor of TMZ-induced thrombocytopenia in malignant glioma patients. The IPF has been described to reflect platelet precursors, and may be considered a parameter for the differentiation and monitoring of several forms of thrombocytopenia including chemotherapy-induced myelosuppression. METHODS: We prospectively included 52 malignant glioma patients receiving TMZ-containing therapy regimens in this study. Platelet counts and IPF were determined at each clinical follow-up visit (weekly during concomitant to radiochemotherapy or at least monthly during adjuvant TMZ monotherapy) using the Sysmex XE-2100 system. RESULTS: The highest combination of sensitivity and specificity was observed for a PLT change per day of ≥0.05 × 10^10/L. At this cutpoint, the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for prediction of significant thrombocytopenia (<100,000/μL) were 80%, 50%, 66%, and 98%, respectively, The
highest combination of sensitivity and specificity was observed for an IFP change of 0.014 percentage-points per day. At this cutpoint, the sensitivity, specificity, PPV, and NPV for prediction of significant thrombocytopenia were 60%, 75%, 67%, and 97%, respectively. CONCLUSIONS: Low sensitivity, specificity, and PPV indicate that the time course of PLT counts and IFP measured at routine clinical follow-up are not useful for prediction of thrombocytopoenia in glioma patients treated with TMZ.

P.050. IDH1 MUTATION IS AN IMPORTANT FACTOR PREDICTING OUTCOME IN HIGH GRADE GLIOMAS
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INTRODUCTION: A recent genome-wide mutational analysis revealed somatic mutations of the isocitrate dehydrogenase 1 gene (IDH1) in gliomas. IDH1 serves as a major source for cytosolic NADPH production necessary for the regeneration of reduced glutathione, which functions as the main antioxidant in mammalian cells. To determine the prevalence and the prognostic impact of IDH1 mutation in gliomas, we investigated a series of these tumors of different WHO grades. In addition, we examined the correlation of IDH1 mutations with MGMT promoter methylation status and overall survival. METHODS: We screened a total of 83 gliomas, including 34 glioblastomas (GB), 5 anaplastic astrocytomas (AA), 3 diffuse astrocytomas (DA), 1 pilocytic astrocytoma (PA), 7 anaplastic oligoastrocytoma (AOA), 3 oligoastrocytoma WHO grade II (OA), 13 anaplastic oligoastrocytoma (AOG), 12 oligodendroglioma WHO grade II (OG), 3 ependymoma (EP), and 1 anaplastic ependymoma (AEP) from the Virgen de la Salud Hospital (Toledo, Spain) by using high-resolution melting (HRM) technology. IDH1 codon 132 sequencing was performed in 31 of these 83 gliomas. MGMT promoter methylation status was analyzed by a nested methylation-specific PCR assay. Log-rank tests and Kaplan–Meier survival curves were performed to analyze the relationship of IDH1 mutational status with overall survival of the patients. RESULTS: We found IDH1 mutations in a total of 36 out of 83 gliomas: 21% (7/34) GB; 60% (3/5) AA; 67% (2/3) DA; 71% (5/7) AOA; 100% (3/3) OA; 61% (8/13) AOG; and 67% (8/12) OG. No mutation was present in any of PA, EP or AEP cases. Sequencing confirmed the results obtained by HRM in all 31 sequenced tumors. Two different mutations were found in codon 132: Arg132His in 19 cases and Arg132Gly in two other cases. Almost all IDH1 mutated gliomas presented MGMT promoter methylation (92%). The presence of IDH1 mutation was correlated with a better outcome in high grade gliomas (P < .01). CONCLUSION: We confirmed the very high frequency of IDH1 mutations in WHO grade II and III astrocytic and oligodendroglial gliomas while the low or absent frequency of mutation in primary GBs and epimelan tumors. In addition, this study, IDH1 mutation is an important factor associated with favorable prognosis.

P.051. MUTATIONS IN IDH1 AND TP53 AS PROGNOSTIC BIOMARKERS IN BULGARIAN PATIENTS WITH GLIOMAS
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Brain tumors, in particular gliomas, are characterized by high mortality rate. However, gliomas with similar features often show different behavior. This raises the issue about molecular markers for prognosis prediction. Recently, somatic mutations in IDH1, which encodes cytoplasmic isocitrate dehydrogenase I, were reported to occur at high frequency in glioblastomas and association with overall survival was found. Genetic aberrations in IDH1 were predominantly detected in tumors that harbor TP53 mutations and mutations at codon 248 and 273 were associated with good prognosis. To determine prognostic value of IDH1 and TP53 mutations in Bulgarian patients, 30 glial tumors of various grades were selected and DNA was extracted from them. All samples were examined by direct sequencing for mutations in exons 4 of IDH1 and exon 5–8 of TP53 gene. Mutations in IDH1 were found in 8 (26.7%) glial tumor. All genetic aberrations were located at position 395 and caused amino acid substitution R132H. Patients with IDH1 mutations were younger (median age 35.5 vs 54 in non-mutated cases; P = .001) and had better overall survival (median survival 32.1 vs 5 months in non-mutated cases; P = .01). Mutations in TP53 were detected in 7 (23.3%) tumor samples. Patients with mutated TP53 showed increase in overall survival (median survival 38.9 vs 5.4 months in non-mutated cases; P = .007). Genetic alterations in TP53 were found in 4 (50.0%) tumors with mutated IDH1 and 3 (13.6%) gliomas without IDH1 mutation. Median survival of patients harboring mutations in both genes was 43.8 months, while median survival of those with mutation in one of the genes and nonmutated cases was 31.6 and 6 months, respectively. Our results indicate that together IDH1 and TP53 mutations identify gliomas with better survival and may be applied as prog nostic biomarkers in Bulgarian patients with gliomas.

P.052. PROMOTOR HYPERMETHYLATION-MEDIATED DOWN-REGULATION OF RUNX3 GENE IN HUMAN BRAIN TUMORS
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Brain tumors are usually caused by a change in genetic structure. Methylation of promoter regions, with corresponding downregulation of gene expression, has been implicated as an alternative mechanism for tumor suppressor gene inactivation. Runt-related (Runx) proteins are tissue-restricted and cancer-related transcription factors that regulate cell proliferation and differentiation. RUNX3, the smallest protein of the Runx family, has been shown to play an important role in neuronal development, localized at 1p36 and its loss leads to tumorigenesis. We aimed to evaluate the methylation-mediated expression regulation of RUNX3 gene in brain tumors. Cases (10 females, 11 males) were recruited into the study that have been diagnosed as brain tumors (3 meningiomas, 3 anaplastic astrocytomas, 3 diffuse astrocytoma, 12 GBM) and taken the decision of surgical operation. The mean age was 52.43 ± 15.33. Explant cell cultures were performed. Total RNA was isolated. Real-time quantitative RT-PCR analyses of RUNX3 gene were actualized. Genomic DNA and the bisulphite modification were performed for DNA methylation analysis. Quantitative methylation-specific PCR was used and primer pairs were designed. There was no significant difference between methylated and unmethylated quantitative ratio of RUNX3 gene promoter region and gene expression relative ratio. Methylated and unmethylated ratio in anaplastic astrocytoma, diffuse astrocytoma, GBM, meningioma, and in all groups were: 1.44, 1.09, 1.51, 1.52 vs 1.43, respectively. One allele was found methylated necessarily. No methylation was detected in GBM and anaplastic astrocytoma groups of one each case. Methylated was no unmethylated promoter in one of the GBM cases. There were significant differences between relative ratio of RUNX3 gene expression and methylated/unmethylated ratio rate, compared with all groups (P = .001) and compared with GBM groups (P = .041). This study overemphasized the RUNX3 gene importance in brain tumors, as a result of the existence at least one methylated allele.

MALIGNANT GLIOMA: CORRELATION BETWEEN SERUM VEGF AND RESPONSE TO TREATMENT
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BACKGROUND: Significant therapeutic benefit has been observed for recurrent malignant glioma (MG) patients treated with bevacizumab (BV), a neutralizing monoclonal antibody against the vascular endothelial growth factor (VEGF). BV decreases VEGF levels and response to BV has never been addressed so far. METHODS: We conducted a prospective analysis of recurrent MG patients treated with BV alone or in combination with chemotherapy performing serial evaluations of serum and plasma VEGF (sVEGF) and VEGF levels and procoagulant factors such as Tissue Factor (TF) and Thrombin/Antithrombin Complex (TAT) plasma levels (ELISA). Baseline, and post-treatment samples were collected at each administration of BV. RESULTS: Eighteen recurrent MGs (glioblastoma = 7, anaplastic astrocytoma = 7, oligodendroglioma = 4) who received BV at 10 mg/kg intravenously every 14 days, of whom 13 in association with chemotherapy were included in the study. Median age was 39 years (27–65), and median
Karnofsky performance status was 80 (60–90). The median number of previous chemotherapy lines was 2 (2–3) and all patients had received prior surgery and radiotherapy. Out of the 12 evaluable, 4 partial responses (33%), 3 stable disease (25%), and 5 disease progresses (42%) were observed. Eight patients showed an improvement in neurological signs and symptoms. Rasal vVEGF lower than <224.25 pg/mL were observed in responding patients. Overall, serum and plasma VEGF, TF, and TAT levels decreased during BV-based therapy. Patients of older age (>40 years) had higher vVEGF and pVEGF levels at baseline compared with the younger ones (<40 years). CONCLUSIONS: BV-based therapy showed activity in patients with heavily pretreated recurrent MGs. Low sVEGF levels at baseline might help predict response in recurrent MG patients treated with BV-based therapy.

P.054. HES6 AS A GLIOMA BIOMARKER WITH FUNCTIONAL SIGNIFICANCE FOR CANCER GROWTH
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Malignant gliomas are the most common type of primary brain tumors affecting 16,000 new patients every year in the United States. In this study, we undertook a systematic large-scale transcriptomic data mining study of 9,783 hybrid samples from the Genesapans database (www.genesapans-s.org) in order to identify the most glioma-specific biomarkers. We searched for genes that were highly expressed in 32 glioblastoma multiforme (GBM) samples and in 66 anaplastic astrocytomas when compared with 425 samples of the normal central nervous system as well as all other normal and cancerous tissues in the database. Transcriptase cofactor HES6 (Hairy and enhancer of split 6) emerged as one of the most glioma-specific genes. Since the role of HES6 in glioma pathogenesis is poorly understood, we could not validate its expression by immunostaining and functional role by siRNA knockdown studies in glioma cell lines. HES6 protein levels were studied in a glioma tissue microarray material that consisted of 414 samples as well as in normal brain tissue controls. Positive HES6 immunoreactivity was present in 99% of available gliomas. Recurrent tumors of grade 2 astrocytomas and grade 2–3 oligoastrocytomas showed higher levels of HES6 immunoreactivity than the corresponding primary tumors. Endothelial cells within the tumors were also stained in 75% of gliomas. In functional studies, cell viability was reduced by 60% and caspase 3/7 activity elevated after HES6 silencing by RNA interference in A172 and LN405 cells. HES6 silencing also increased apoptosis 2-fold in 2 cell lines as measured by Apo-ONE Homogeneous Caspase-3/7 Assay. The biological role and consequences of HES6 silencing was explored with genome-wide analyses following RNAi, which indicated a key role for HES6 in, for example, p53, c-myc, and CREB1 transcriptional networks. Gene ontology analysis implicated genes involved in cellular movement, development, and RNA posttranscriptional modification. HES6 protein was localized to the PML bodies by immunostaining and co-localized with the creb-binding protein (CBP). In conclusion, these results pinpointed HES6 as a potential therapeutic target playing a critical role in sustaining glioma cell growth, survival and possibly invasion. HES6 may also be a useful biomarker for gliomas.

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NEW DRUG DELIVERY METHODS
P.054*. GH5-CONJUGATION IMPROVES EFFICACY OF DOXIL AGAINST INTRANARCALXENOGRAFTS
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High-grade glioma is a uniformly fatal disease with an unmet need for better therapy. A major reason for this poor outcome is the invasive nature of gliomas. Novel therapies that target invasive brain tumor cells should be invented, but a major impediment to the delivery of adequate amounts of therapeutics is the blood–brain barrier (BBB), which is largely intact in regions where invasive cells reside. Glutathione (GSH)-conjugated PEGylated liposomes may be suitable vehicles for targeted delivery of small molecule cytotoxic drugs across the BBB. GSH is a natural antioxidant that is found at high levels in the brain and its active transporter is abundantly expressed at the BBB. Previous studies using microanalysis with an increasing % of GSH conjugated to liposomes carrying ribavirin have shown a 5% GSH-dependent increase of drug levels in brain interstitial fluid (up to 5-fold higher), and GSH-liposomes carrying endomorpin-1 were more effective in hot-plate tests when compared with unconjugated liposomes. We have now tested GSH-conjugated PEGylated liposomes containing doxorubicin (GSH-Doxil) for treatment of mice carrying intracranial U87 xenografts. In a first series, we compared 5% GSH-Doxil to conventional Doxil, free doxorubicin (Dx), and untreated controls. Mice were injected with 10 × 5 U87-luc cells and bioluminescence (BL) imaging was used for follow-up. After 11 days, mice were stratified into control or test groups (n = 9 / group). Mice received 3 consecutive weekly dosing of 5 mg/kg Doxil equivalents. The cohorts receiving Doxil and Dx showed a marginal growth delay relative to controls. The response with 5% GSH-Doxil was more promising but variable; two animals receiving 5% GSH-Doxil showed complete regression, which was not observed in any of the other cohorts, whereas other tumors in this cohort responded more similar to the other treatment groups. Since the treatment was well tolerated, we performed another more dose-intense series, administering biweekly 5 mg/kg Doxil equivalents. Moreover, 5%GSH-Doxil and 5%GSH-Doxil were tested relative to Doxil and untreated controls. Treatment started at Day 14 after tumor cell injection, stratifying only animals whose tumor BL signals increased relative to Day 11. After Day 25, the animals experienced weight loss 2 weeks after stratification. In this series, the variation in tumor response was small. There was one complete regression in the cohort of 5% GSH and not in any of the other cohorts. Moreover, the growth delay in the other tumors in this 5% GSH-Doxil cohort was significantly longer than in any of the other cohorts. This growth delay was correlated to a significantly increased median survival of 32.5 days relative to 27 days for untreated controls. The response in the 5% GSH and Doxil cohorts was marginally better relative to controls Overall, these results warrant further preclinical and clinical investigation using 5% GSH-Doxil liposomes.

NEUROIMAGING OF BRAIN TUMORS
P.056*. ROUTINE FOLLOW-UP IMAGING AFTER TREATMENT FOR GLOBLASTOMA: HOW USEFUL IS IT?
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INTRODUCTION: Glioblastoma multiforme (GBM) is the most common and aggressive malignant brain tumor (primary brain tumor [PBT]). The common practice in Neuro-Oncology centers to use cranial imaging in the posttreatment follow-up of patients diagnosed with GBM. However, there is little published guidance regarding the recommended timing and frequency of follow up imaging, with little consensus regarding the efficacy of imaging in detecting asymptomatic tumor recurrence. OBJECTIVES: Our local Neuro-Oncology guidance recommends that patients diagnosed with GBM are CT scanned at 3 months (defined as 12 ± 2 weeks) post treatment and thereafter at 3 monthly intervals. This audit assessed compliance with local guidelines and performance in detecting asymptomatic recurrence.

METHODS: Retrospective review of case notes. Data collected regarding post treatment imaging, explained in part by high patient mortality (median survival 35 weeks from time of diagnosis) and the proportion of patients receiving palliative care where follow up imaging was not indicated. Two hundred sixty-five cases were analyzed. 55 (35%) patients did not receive any follow-up imaging, explained in part by high patient mortality (median survival 35 weeks from time of diagnosis) and the proportion of patients receiving palliative care where follow up imaging was not indicated. Two hundred sixty-five cases were analyzed. 55 (35%) patients did not receive any follow-up imaging, explained in part by high patient mortality (median survival 35 weeks from time of diagnosis) and the proportion of patients receiving palliative care where follow up imaging was not indicated. Two hundred sixty-five cases were analyzed. 55 (35%) patients did not receive any follow-up imaging, explained in part by high patient mortality (median survival 35 weeks from time of diagnosis) and the proportion of patients receiving palliative care where follow up imaging was not indicated.

RESULTS: One hundred sixty-two patients diagnosed with GBM were identified between 2004 and 2008. One hundred fifty-six cases were analyzed. 55 (35%) patients did not receive any follow-up imaging, explained in part by high patient mortality (median survival 35 weeks from time of diagnosis) and the proportion of patients receiving palliative care where follow up imaging was not indicated. Two hundred sixty-five cases were analyzed. 55 (35%) patients did not receive any follow-up imaging, explained in part by high patient mortality (median survival 35 weeks from time of diagnosis) and the proportion of patients receiving palliative care where follow up imaging was not indicated.

CONCLUSIONS: Routine follow-up imaging is not indicated in the majority of patients treated for GBM. The National Institute for Clinical Excellence (UK) and the European Society for Medical Oncology recommend the use of cranial imaging in MPBT follow up, stating 3–4 monthly scans is ‘common practice’. Neither specifies the optimal timing or frequency of post treatment scans. The National Comprehensive Cancer Network (USA) recommends post treatment scans every 2–3 months post MBPT treatment, as does the Cancer Council Australia. There is lack of consensus and evidence regarding the recommended treatment imaging in patients with MPBT. Further studies are required to evaluate clinical and cost effectiveness.
BACKGROUND: During the follow-up of brain tumor patients, the appearance of new contrast-enhancing lesions on MRI frequently occurs. Disease progression. However, conditions such as early or delayed radiation necrosis can mimic tumor progression and are important to recognize to avoid futile therapeutic escalation. Transient peri-ictal MRI changes have been described in epileptic patients and some reports have suggested that these changes can also mimic disease progression in brain tumor patients. However, the clinical and MRI features of these patients have not been specifically studied yet. METHODS: The databases of four institutions were consulted to identify brain tumor patients who presented during the follow-up period transient MRI lesions wrongly suggesting tumor progression in a context of epileptic seizures. RESULTS: Seven patients were identified. Five patients suffered from high-grade gliomas, one from a medulloblastoma and one from a single brain metastasis. All patients had been initially treated with surgery and radiotherapy and all had achieved a complete remission. The peri-ictal pseudo-progression episode occurred after a mean delay of $13.3 \pm 8.6$ years after radiotherapy (range 3–25). All patients demonstrated new focal neurological signs in a context of frequent epileptic seizures. The MRI features were highly similar across patients and consisted of focal cortical and/or leptomeningeal enhancing lesions that could extend beyond the initial tumor localization. The clinical situation progressively improved after adjustment of antiepileptic drugs and transient oral corticotherapy. MRI was normalized at 3 months in 4 patients and at 6 months in the others. Three patients demonstrated two or more relapses with the same clino-radiological pattern. At last follow-up, after a mean period of $3.7 \pm 2.3$ years (range 1–7) since the initial peri-ictal pseudo-progression episode, none of the patients had presented a tumor recurrence. CONCLUSIONS: In brain tumor patients, especially in long-term survivors treated with radiotherapy, the appearance of new cortical and/or leptomeningeal contrast enhancing lesions in a context of seizures should raise the suspicion of pseudo-progression. We make the hypothesis that this phenomenon is in relation with a post-ictal cortical vasculopathy.

P.057*. PERI-ICTAL PSEUDO-PROGRESSION IN BRAIN TUMOR PATIENTS S. Rheims, F. Ducray, L. Taillandier, D. Ricard, V. Bourg, V. Desestret, S. Cartalat-Carel, M. Sanson, and J. Honnorat; 1Service de Neurologie B, Hospices Civils de Lyon, Lyon, France; 2Neuro-oncology Unit, Department of Neurology, Hôpital Central, Centre Hospitalier Universitaire de Nancy, Nancy, France; 3Service de Neurologie, Hôpital du Val-de-Grâce, Paris, France; 4Service de Neurologie, CHU Hôpital Pasteur, Nice, France; 5Fédération de Neurologie Mazzarin, Groupe Hospitalier Pitié-Salpêtrière, Paris, France

BACKGROUND: Glioblastoma is a highly angiogenic tumor. Therapy with the monoclonal anti-vascular endothelial growth factor (VEGF) antibody bevacizumab aims at inhibiting neo-angiogenesis and has shown promising results in phase II trials in recurrent glioblastoma. However, the effect of bevacizumab has not been adequately investigated in vivo so far. In this study, we analyze the effect of bevacizumab therapy on recurrent glioblastoma and the vasculature using high-resolution magnetic resonance imaging (MRI) at 7 Tesla including susceptibility-weighted imaging (SWI). METHODS: We performed repeated 7-Tesla MRI investigations in 4 male and 2 female patients with recurrent glioblastoma receiving bevacizumab therapy. MRI investigations were performed at baseline and 2, 4, and 8 weeks after start of treatment. Each MRI measurement was performed within 48 hours before bevacizumab administration. A three-dimensional, fully-first-order flow-compensated gradient-echo sequence with a TE of 15 ms was performed to acquire SWI data. T1-weighted data were acquired using an MP-RAGE sequence with the following parameters: image-matrix $= 320 \times 320$, resolution $= 0.75 \times 0.75 \times 0.7$ mm, slice $= 208$; parallel imaging factor $= 2$, TR/TI/TE $= 3800/1700/3.55$ ms, acquisition time $= 10.25$ minutes. Contrast agent was injected in the arterial phase in T1-weighted measurement. RESULTS: Image quality was in general excellent, although in few investigations image quality was impaired by movement artifacts caused by neurological symptoms. In 3 of 6 patients we found marked and rapid decrease of brain edema after initiation of bevacizumab therapy. In 2 patients we observed an increase of SWI signals already at the first follow-up MRI 2 weeks after initiation of bevacizumab therapy. Both patients developed progressive neurological worsening and bevacizumab therapy had to be suspended because of tumor progression after 6 and 8 weeks, respectively. In 1 patient showing rapid decrease of contrast enhancement and sustained clinical improvement under bevacizumab therapy, with SNHL. Hypointensity of the affected labyrinth will result in a significant faster deterioration of PTA. Audiological deterioration occurs irrespective of VS growth and significant growth during the first year of FU predicts further growth during FU. No other factors predicting growth were identified, therefore sequential MRIs remains the only objective FU method of conservatively followed vs Volume measurements are not a reliable measure predicting auditory function, in a W&S policy. These findings can aid the clinician dealing with VS patients in a W&S policy.

P.059*. MRI AND THALLIUM-201 SPECT IN THE PREDICTION OF OUTCOME IN GLIOMA THERAPY J. M. Jos, J. Berkhof, O. S. Hoekstra, I. Bosma, E. M. Sizoo, J. J. Hemans, J. C. Reijnveld, E. Sanchez, F. J. Lagerwaard, J. Butter, D. P. Noske, and J. T. Postma; VU University Medical Center, Amsterdam, Netherlands

BACKGROUND: The prediction of outcome and the detection of tumor progression in glioma patients are of great clinical importance. In previous studies, we found 201Tl SPECT to be superior to conventional CT and MRI in the prediction of outcome during chemotherapy for recurrent glioma. The present study aims to study the value of MRI and 201Tl SPECT in the prediction of outcome in glioma patients treated with temozolomide and radiotherapy to optimize tumor follow-up. METHODS: We included patients treated with temozolomide chemotherapy for newly diagnosed glioblastoma multiforme (GBM) (study A), and with temozolomide for recurrent glioma (study B). MRI and 201Tl SPECT scans were obtained at regular intervals. The value of both imaging modalities in predicting overall survival (OS) and progression-free survival (PFS) were examined using Cox regression analyses. RESULTS: Altogether 138 MRI and 113 201Tl SPECT scans in 46 patients were performed. Both imaging modalities were strongly related to OS and PFS. In study A, the predictive capacity of MRI and 201Tl SPECT increased during treatment. In study B, baseline measurements appeared strongly predictive of outcome. The addition of one modality to the other did not contribute to the prediction of outcome. CONCLUSIONS: Both MRI and 201Tl SPECT are valuable in the prediction of outcome. It is adequate to restrict to one of both modalities in the radiological follow-up during treatment. Without clinical progression, we suggest to perform MRI only at the end of the standard treatment protocol in newly diagnosed GBM, and only at baseline in recurrent glioma.

P.060*. ANALYZING RESPONSE OF MALIGNANT GLIOMA TO BEVACIZUMAB USING HIGH-RESOLUTION MAGNETIC RESONANCE IMAGING AT 7 TESLA G. Grabner, I. Nöhauer, K. Eladý, C. Marosi, S. Trattning, and M. Preusser; Medical University of Vienna, Vienna, Austria

BACKGROUND: Glioblastoma is a highly angiogenic tumor. Therapy with the monoclonal anti-vascular endothelial growth factor (VEGF) antibody bevacizumab aims at inhibiting neo-angiogenesis and has shown promising results in phase II trials in recurrent glioblastoma. However, the effect of bevacizumab has not been adequately investigated in vivo so far. In this study, we analyze the effect of bevacizumab therapy on recurrent glioblastoma and the vasculature using high-resolution magnetic resonance imaging (MRI) at 7 Tesla including susceptibility-weighted imaging (SWI). METHODS: We performed repeated 7-Tesla MRI investigations in 4 male and 2 female patients with recurrent glioblastoma receiving bevacizumab therapy. MRI investigations were performed at baseline and 2, 4, and 8 weeks after start of treatment. Each MRI measurement was performed within 48 hours before bevacizumab administration. A three-dimensional, fully-first-order flow-compensated gradient-echo sequence with a TE of 15 ms was performed to acquire SWI data. T1-weighted data were acquired using an MP-RAGE sequence with the following parameters: image-matrix $= 320 \times 320$, resolution $= 0.75 \times 0.75 \times 0.7$ mm, slice $= 208$; parallel imaging factor $= 2$, TR/TI/TE $= 3800/1700/3.55$ ms, acquisition time $= 10.25$ minutes. Contrast agent was injected in the arterial phase in T1-weighted measurement. RESULTS: Image quality was in general excellent, although in few investigations image quality was impaired by movement artifacts caused by neurological symptoms. In 3 of 6 patients we found marked and rapid decrease of brain edema after initiation of bevacizumab therapy. In 2 patients we observed an increase of SWI signals already at the first follow-up MRI 2 weeks after initiation of bevacizumab therapy. Both patients developed progressive neurological worsening and bevacizumab therapy had to be suspended because of tumor progression after 6 and 8 weeks, respectively. In 1 patient showing rapid decrease of contrast enhancement and sustained clinical improvement under bevacizumab therapy, with SNHL. Hypointensity of the affected labyrinth will result in a significant faster deterioration of PTA. Audiological deterioration occurs irrespective of VS growth and significant growth during the first year of FU predicts further growth during FU. No other factors predicting growth were identified, therefore sequential MRIs remains the only objective FU method of conservatively followed vs Volume measurements are not a reliable measure predicting auditory function, in a W&S policy. These findings can aid the clinician dealing with VS patients in a W&S policy.
therapy, SWI signals remained unchanged at all 7-Tesla MRI investigations. CONCLUSIONS: High-resolution 7-Tesla MRI is feasible in patients with malignant glioma. Our data indicate that in a fraction of recurrent glioblastoma patients early growth of tumor vasculature occurs despite bevazumab therapy (“primary bevazumab resistance”). Advanced imaging modalities may improve assessment of response to bevazumab therapy.

P.061*. VALUE OF THALLIUM SPECT (SPECT) TO EVALUATE RESPONSE TO BEVAZUMAB TREATMENT IN HIGH-GRADE GLIOMA (HGG) PATIENTS

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OBJECTIVES: To analyze whether Thallium-SPECT is a good method to evaluate response to bevacizumab in recurrent HGG patients. METHODS: Seventeen patients with recurrent HGG who were considered for treatment with bevacizumab + irinotecan (Bev + Ir) were studied with a SPECT and MRI, and then re-assessed after treatment. In order to evaluate response correlation. PATIENT CHARACTERISTICS: Twelve out of 17 patients could be evaluated with both techniques: 11 men and 6 women; 16 patients had previous positive SPECT; 4 patients progressed before imaging evaluation. Male/female ratio was 9/3. There were 10 GBMs out of 12. Previous surgery was biopsy in 5 cases, and partial or complete resection in 7. Regarding previous treatment, Stupp regimen was administered in 6 cases. Number previous chemotherapy lines ≥2 were 7/12. KPS >60% was in 11/12 and Barthel I ≥60% in 11/12. Evaluated treatment was as follows: Bev 2/12 or Bev and Ir 10/12. RESULTS: Response rate by MRI was as follows: P 41.7%, SD: 8.3%, PR: 25%, CR: 8.3%. Coincidence between SPECT and MRI was 41.7%, and CR: 8.3%. Response rate by SPECT was as follows: P 16.7%, SD: 8.3%, PR: 16.7%, CR 25%. Response by modified MacDonald criteria: P: 58.3%, SD: 8.3%, PR: 25%, CR: 8.3%. Coincidence between SPECT and MRI was 24.9% and SPECT with MacDonald’s criteria was 16.6%. The sole patient with a CR by MRI and MacDonald’s modified criteria had a normalization of a previous positive SPECT lasting for 103+ weeks while continuous maintenance Bev. CONCLUSIONS: In spite of reduced number of patients, it seems that Thallium SPECT is not a good imaging method to evaluate response of bevacizumab treatment.

P.062*. PRESERVATION OF PYRAMIDAL TRACT BY NAVIGATION-ASSISTED INTRAOPERATIVE MAPPING IN GLIOMA SURGERY

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OBJECTIVE: The preservation of pyramidal tract is essential and very important issue to maintain the patients’ quality of life. Recent technologies such as tensor-image of MRI and neuronavigator are unreliable method for precise identification as a result of intraoperative brain shift. Electrical stimulation of the resected tumor cavity has been a gold standard; however, it sometimes results in postoperative neurological deterioration. We developed a novel method to identify and protect the motor fiber during tumor resection. METHODS AND RESULTS: NY Tract Finder II, a new electrode designed for navigation-assisted detection of motor tract in cerebral white matter, was used during the resection of glioma adjacent to pyramidal tract. The bipolar needles are insulated except those tips and marked off in millimeters. The electrode was inserted into the cerebral white matter with guidance by a neuronavigator with continuous electrical stimulations. The muscle-motor evoked potentials were recorded to alert surgeons to the existence of motor fibers. In the recent cases, tractography images were integrated into the neuronavigation system and compared with intraoperative neurophysiological data. This technique enabled the detection of the pyramidal tract adjacent to glioma. The depth of pyramidal tract from the wall of tumor resected cavity could be measured by the ruler on the needles. There were discrepancies between tractography data integrated into neuronavigator and actual neurological localization of pyramidal tracts. Postoperative MRIs revealed that the tumors were resected close to the primary motor cortices and pyramidal tracts even with brain shifts. None of the patients presented postoperative neurological deterioration. CONCLUSIONS: This technique may be a feasible method to detect and spare the motor pathways even with brain shifts. The combination of 2 modalities is easy-to-use technique in the glioma surgery in eloquent brains.

P.063*. MAGNETIC RESONANCE IMAGING OF VIRAL SPREAD AND INTRATUMORAL INFLAMMATION DURING ONColytic VIROTHERAPY

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One of the major drawbacks in treating gliomas is the poor efficiency of drug delivery. Oncolytic viruses (OVs) that can selectively replicate in tumor cells and potentially can reach the infiltrating margins of the tumor, represent a promising tool to overcome this problem. However, the in vivo therapeutic benefit of OVs is M.O.G.l. because of host factors. We have recently demonstrated that the capacity of OVs to spread in vivo through the tumor is inhibited by intratumoral infiltration of phagocytic microglia and peripheral macrophages. Combining OVs with immune suppressive drugs can therefore increase their spread and therapeutic efficacy. However, the lack of a noninvasive imaging technique to detect intratumoral OV spread and phagocytic infiltration constitutes an important limitation in evaluating the results of new therapeutic strategies. We have tested 2 noninvasive magnetic resonance imaging techniques. The first one uses a gadolinium-based contrast agent to detect myeloperoxidase (MPO) activity, an enzyme present in phagocytic cells. MRI images show increased MPO activity after OV delivery. This enzymatic activity is reduced when animals are pretreated with cyclophosphamide. The MRI data correlate with immunohistostaining of MPO, and size, and in the center of the tumor can be distinguished and provides us with information on tumor shape, size, and thus we conclude that MRI can serve as an imaging of the spatio-temporal distribution of replicating agents (ie, OVs), through the use of artificial peptides presenting magnetic contrast through chemical exchange saturation transfer (CEST). We have thus generated an OV arm with a novel reporter gene to be used in brain tumor virotherapy. Because these two technologies can be combined, together they will provide a powerful diagnostic tool to monitor efficacy of OVs and glioma response to virotherapy, thus leading to the design of efficient strategies of virotherapy that overcome the influence of host factors.
INTRODUCTION: Assessment of therapeutic efficiency for glioblastoma (GB) patients is traditionally accomplished by measuring changes in tumor size, as defined by the Response Evaluation Criteria in Solid Tumors (RECIST) at 10 weeks after initiation of treatment. One disadvantage of size measures is the duration for changes to occur, with 10 weeks necessary to assess the response. The functional diffusion map (fDM) which is a new imaging assessment of GB patients was reported by Hamstra et al. This fDM analysis is able to assess at 3 weeks after initiation of treatment earlier than the traditional imaging assessment. In this study, we evaluated GB patients treated by boron neutron capture therapy (BNCT) by using this fDM analysis. MATERIALS AND METHODS: During 2003–2007 period, 17 patients with GB treated by BNCT were retrospectively enrolled onto a study of intratreatment MRI at 2 and/or 7 and/or 14 days, and/or 10 weeks. We used $I_{\text{Response}}^{3T}$ and fDM analysis that is analysis software to be able to assess changes over time of apparent diffusion coefficient (ADC) values. Results and Discussion: The volume of tumor with decrease diffusion analyzed by fDM at 2 days was the strongest predictor of patients survival time since BNCT ($R^2 = 0.7433$). Our study showed that greater decreases in ADC value in response to BNCT over time were observed in the good prognosis patients compared with the poor prognosis patients. The decrease in ADC value in response to BNCT at an acute stage was caused by BNCT as a high-dose radiation therapy, unlike a conventional radiotherapy as a low-dose radiation therapy. Briefly, BNCT might cause tumor cells to swell in an acute stage by the high-dose radiation therapy. Further, the fDM analysis captured it as an imaging of fDM. CONCLUSION: The fDM analysis could provide an earlier imaging assessment of GB patients treated by BNCT. Early detection of treatment failure can also allow more intensive therapy in patients with the worst prognoses. This fDM analysis will have the potential to replace size measures. Therefore, we will assess many more the number of GB patients and perform further animal experiments.

INTRODUCTION: We present a multilinear brainstem lesion, in conjunction with a right temporal mass, which turned out to be an astrocytoma. To our knowledge, this kind of presentation has not been described so far. CASE DESCRIPTION: A 51-year-old male patient presented at the neurology department with dizziness, speech disturbances and a strange feeling at the left side of his face. Initial neurological examination was unremarkable, except for a dysarthria. One day after the MRI scan was performed, the patient was admitted to the emergency department because of a secondary generalized seizure. Neurological examination revealed a (post ictal) left sided paralysis and a Babinski-reflex at the left side. In the following days and weeks, there was progressive neurological deterioration with progressive dysarthria, swallowing disturbances, diplopia as a result of abducens paresis and a left-sided hemiparesis. Laboratory results of blood and CSF were unremarkable. No signs of infection were present. Lues, Neuroborreliosis, HIV, Ebstein–Barr, Herpes encephalitis were ruled out. CSF showed no pleiocytosis or signs of malignancy. MRI showed a T2 hyperintense mass in the right temporal lobe, without enhancement after administration of gadolinium; radiologically suggestive of a low-grade glioma. Furthermore, hyperintensity along the white matter tracts in brainstem, pons, cerebellar peduncle, and thalamus was present. This white matter hyperintensity exerted some mass effect and enhanced partially, namely in the right-sided brainstem. Repeated MRI scan 2 weeks later showed progression of the hypointens tracts, now extending into the left pons en cerebellar peduncle. The patient underwent a navigation-guided biopsy of the right temporal lesion. Pathological examination showed a diffuse infiltrating neoplasm of astrocytic origin with high cellularity and increased proliferation index. No tumor necrosis or microvascular proliferation was seen. A high-grade (WHO grade III) anaplastic astrocytoma of the temporal lobe and brainstem was concluded. Patient deteriorated further and palliative treatment was offered. CONCLUSION: The presented case is a radiological illustration of a high grade glioma diffusely infiltrating the white matter tracts in brainstem, pons and thalamus, thereby visualizing the normal anatomical connections. This rare presentation should be recognized to prevent unnecessary delay in establishing the diagnosis.

GLOBLASTOMA MULTIFORME AND ANAPLASTIC GliOMAS

P.069*. PROGNOSTIC IMPACT OF STEM CELL MARKER CD133 IN GLOBLASTOMA PATIENTS TREATED WITH CONCOMITANT RADIOTHERAPY: A PROSPECTIVE STUDY
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Cancer stem cells (CSC) are thought to represent the population of tumorigenic cells responsible for tumor development. The CD133
antigen has been described as a putative stem cell marker in malignant brain tumor that could identify such a tumorigenic population in a subset of glioblastoma multiforme (GBM). To date, the correlation between CD133 expression in primary GBM and patients’ prognosis is not clearly established. To address this question we investigated the relationship between the quantitative expression of CD133 stem cell antigen mRNA using real-time RT-QPCR and patient outcome in a prospective cohort of 61 primary GBM patients treated with radiotherapy combined with concomitant and adjuvant therapy with temozolomide. On multivariate survival analysis, CD133 stem cell antigen expression was a significant (P = .007) prognostic factor for adverse overall-survival independent of extent of resection (P = .012), patient age (P = .037), and MGMT status (P = .002). Furthermore, according to the combined expression of CD 133 and MGMT status, the patients were categorized into three groups. Among these three groups, patients with methylated tumors and low expression level of CD 133 (group I) had the best prognosis, whereas patients with high expression level of CD 133 (group III) had the poorest prognosis and another group (II) had an intermediate outcome. These findings constitute conclusive evidence that the measurement of the mRNA expression of CD133 stem cell antigen carried by some GBM cancer stem cells actually impact the survival of GBM patients, lending support to the current brain tumor stem cell hypothesis.

P.070*. PATTERN OF RECURRENTITY AND PSEUDO-PROGRESSION IN Glioblastoma Patients Treated With Postoperative Radiotherapy With Concurrent Temozolomide


BACKGROUND: Combined postoperative therapy with temozolomide (TMZ) has demonstrated improvement in disease-free survival of glioblastoma multiforme (GBM). Pseudo-progression is often observed since the introduction of this concurrent regimen. The objective of this study is to compare the incidence of pseudo-progression, pattern of recurrence, and overall survival (OS) in patients treated before and after introduction of concurrent TMZ in this indication. METHODS: A retrospective review was conducted of all pathologically proven GBM cases treated postoperatively in our center between 2004 and 2008. OS was calculated from the time of diagnosis. Pseudo-progression was examined by two different criteria. The first strict criteria define pseudo-progression as ≥25% increase in tumor size or the occurrence of a new contrast-enhancing lesion, with, in absence of new active treatment, either subsequent spontaneous regression to baseline or smaller, or pathologically proven tumornecrosis in absence of new active treatment, either subsequent spontaneous regression to baseline or smaller, or pathologically proven tumornecrosis in absence of new active treatment, either subsequent spontaneous regression to baseline or smaller, or pathologically proven tumornecrosis in absence of new active treatment, either subsequent spontaneous regression to baseline or smaller, or pathologically proven tumornecrosis in absence of new active treatment, either subsequent spontaneous regression to baseline or smaller, or pathologically proven tumornecrosis in absence of new active treatment, either subsequent spontaneous regression to baseline or smaller, or pathologically proven tumornecrosis in absence of new active treatment, either subsequent spontaneous regression to baseline or smaller, or pathologically proven tumornecrosis in absence of new active treatment, either subsequent spontaneous regression to baseline or smaller, or pathologically proven tumornecrosis in absence of new active treatment, either subsequent spontaneous regression to baseline or smaller, or pathologically proven tumornecrosis in absence of new active treatment, either subsequent spontaneous regression to baseline or smaller, or pathologically proven tumornecrosis in absence of new active treatment, either subsequent spontaneous regression to baseline or smaller, or pathologically proven tumornecrosis in absence of new active treatment, either subsequent spontaneous regression to baseline or smaller, or pathologically proven tumornecrosis in absence of new active treatment, either subsequent spontaneous regression to baseline or smaller, or pathologically proven tumornecrosis. The log-rank test was used to evaluate the significance of the prognostic variables, and the Cox model to ascertain any association between PFS and OS. RESULTS: A total of 150 patients (median age: 52 years, [24–76 years]) were enrolled. MGMT methylation status, evaluable in 110 patients, was present in 38% of cases. Median OS was 18.5 months. At disease progression, 40 patients (27%) received temozolomide, 92 patients (61%) received nitrosourea-based-chemotherapy, and 18 patients (12%) received other treatments. At the time of recurrence, median OS was 2.5 months (95% CI: 2.0–3.1), PFS 6.5 months (95% CI: 5.9–7.1), mOS 7.6 months (95% CI: 6.9–8.3) and OS 6.4 months (95% CI: 5.6–7.2%). In the Cox proportional hazard model, PFS with the second-line treatment was correlated with OS measured from the start of the second-line treatment (P < .0001).

CONCLUSIONS: The findings made in the present study, the first in literature to evaluate outcome endpoints for a second-line treatment after RT/TMZ in GBM, provide a strong and substantial argument for active cytoxic drugs in phase II studies on recurrent GBM. For antiangiogenic compounds, OS can be considered as a sound endpoint.

P.072*. A PHASE III RANDOMIZED CONTROLLED TRIAL OF CONCURRENT RADIO-THERAPY WITH CONCOMITANT AND ADJUVANT TEMOZOLOMIDE IN ELDERLY PATIENTS WITH Glioblastoma Multiforme

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INTRODUCTION: The EORTC (26981-22981)/NCIC CTG (CE.3) RCT in newly diagnosed GBM found sustained improvement in survival with the addition of concomitant and adjuvant temozolomide (TMZ) to radiotherapy (RT). Study patients were aged 18–70 (median 56 years), and the main endpoint analysis was powered for a 33% improvement in median survival (increased MST from 6 to 8 months) between arms, using a two-sided 5% alpha, a minimum of 520 deaths must be observed prior to final analysis. A recent RCT in elderly GBM patients found improved survival with RT compared with supportive care alone and another study detected equivalence of 40 Gy/15 vs a 60 Gy/30 RT regimen. Therefore, RT alone is considered standard for elderly patients and 40 Gy/15 is supported as an acceptable fractionation scheme. However, the question remains: does the addition of TMZ to RT confer a survival advantage in elderly patients for whom “short-course” radiotherapy is recommended? Study Design: In order to have 90% power to detect a 33% improvement in the primary outcome of overall survival, yielding a study duration of 5 years. Study Progress: The trial is open in Canada (NCIC CTG), Europe (EORTC), Australia and New Zealand (TROG), and Japan. As of March 1 2010, 123 patients were randomized. Median...
P.073*. INFLUENCE OF HYPOXIA ON GLIOMA AND GLIOMA STEM-LIKE CELLS
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Glioblastoma multiforme (GBM) is the most common brain tumor but also the most aggressive one. Despite heavy treatment, life expectancy usually does not exceed 15 months. Therapy failure may be explained by GBM features such as high proliferation rate, invasiveness, and cellular heterogeneity. Similar to other malignant tumors, GBM appear to contain a subpopulation of cells that display stem cell properties and are able to survive in a hypoxic microenvironment. However, the mechanisms permitting stem-like cell proliferation under low oxygen conditions are poorly understood. Here we provide a detailed functional and molecular analysis of glioma stem-like cells grown under hypoxic conditions. Two stem cell–like cell lines NCH644 and NCH421k were compared with classical serum-dependent glioma cells (U87, U251, and U373) with regard to their behavior less than 1% and 0.1% O2 culture conditions: proliferative potential, invasiveness, and clonogenicity were investigated. Stem cell–like cells showed marked differences in their response to hypoxic conditions as compared with non-stem–like glioma cells. Low oxygen levels dramatically inhibited glioma cell division whereas stem cell–like cell proliferation was only marginally affected by hypoxia. These cells appeared to survive even when oxygen level was as low as 0.1%. The optimal hypoxia conditions were chosen for further transcriptomic analysis based on cell survival data and protein expression profile of hypoxia inducible factor (HIF-1Î±). The cellular response to hypoxia was studied at the transcriptomic level using whole-transcript expression analysis (GeneChip® Human Gene 1.0 ST, Affymetrix). Candidate genes for cell survival response to hypoxia were validated using quantitative PCR, protein-based approaches, and functional bioassays. Such genes may provide new molecular targets for GBM treatment by specifically targeting the glioma stem-like cell population.

INTRODUCTION: We previously demonstrated that NG2 expressing (NG2+) cells in glioblastoma (GBM) exhibit robust proliferative and tumorigenic activity and share phenotypic and functional similarities with NG2 expressing glial progenitors. Here, we conducted comparative studies to address the difference of the molecular signature of GBM-NG2+ and GBM-NG2– cells. METHODS: ACGC2, an immortalized human astrocyte cell line, was used to generate NG2 expressing GBM-like cell lines. Neuron–like cell lines NCH644 and NCH421k were compared with classical serum-dependent glioma cells (U87, U251, and U373) with regard to their behavior less than 1% and 0.1% O2 culture conditions: proliferative potential, invasiveness, and clonogenicity were investigated. Stem cell–like cells showed marked differences in their response to hypoxic conditions as compared with non-stem–like glioma cells. Low oxygen levels dramatically inhibited glioma cell division whereas stem cell–like cell proliferation was only marginally affected by hypoxia. These cells appeared to survive even when oxygen level was as low as 0.1%. The optimal hypoxia conditions were chosen for further transcriptomic analysis based on cell survival data and protein expression profile of hypoxia inducible factor (HIF-1Î±). The cellular response to hypoxia was studied at the transcriptomic level using whole-transcript expression analysis (GeneChip® Human Gene 1.0 ST, Affymetrix). Candidate genes for cell survival response to hypoxia were validated using quantitative PCR, protein-based approaches, and functional bioassays. Such genes may provide new molecular targets for GBM treatment by specifically targeting the glioma stem-like cell population.

P.074*. CIRCULATING ENDOThelial CELLS DECREASE SIGNIFICANTLY IN RELAPSING HIGH-GRADE GILOMA PATIENTS RESPONDING TO BEVACIZUMAB
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Angiogenesis, the recruitment of new blood vessels, is an essential component of tumor progression. High-grade gliomas (HGGs) are highly vascularized tumors and bevacizumab, a humanized monoclonal antibody targeting the vascular endothelial growth factor (VEGF), is active in preclinical testing in vitro and in vivo. In the clinical setting, in combination with irinotecan, other chemotherapy agents or alone, it has shown significant activity in HGG patients. Therefore, the identification of patients who might benefit from antiangiogenic therapies is crucial for the optimization of treatment strategies. In other solid tumors, levels of circulating endothelial cells (CECs) and levels of circulating progenitors (CEPs), contributing to the formation of tumor vessels, correlate with the degree of tumor angiogenesis or the response to angiostatic therapy. Twenty-seven patients with recurrent HGG (22 glioblastomas (GBM) and 5 anaplastic astrocytomas (AA)) were treated at the Neurological Institute C. Besta, Milano, with irinotecan (340 or 125 mg/m2 for patients on EIAEDs or not, respectively) and bevacizumab 10 mg/kg every 2 weeks. Median age was 53 years (range 15–66) and median Karnofsky Performance Status (KPS) was 70 (range 50–100). The median number of prior chemotherapy treatments was 2 (range 1–4). Median follow-up was 6 months. Number and viability of CECs and CEPs were measured on Day 0 and every 2 months by 6-color flow cytometry. CECs were enumerated as CD45-CD31+/P1h12+ cells, whereas CEPs as CD31+/P1h12+/CD45-CD31+/CD133+ cells. CEC subpopulations were defined as CD109+ and CD109−. No severe side-effect was observed during treatment. The first MRI, 2 months after treatment onset, showed progressive disease in 6 subjects, partial response in 16, and stable disease in 4; 1 patient was lost to follow-up. Overall, 6M-PFS was 50% and 6M-OS was 64%. Median PFS and median OS were 6 and 10 months, respectively. For GBM patients, 6M-PFS was 37% and 6M-OS was 65%. At baseline the number of CECs was significantly higher in GBM patients than in AA (113.1 ± 57.7 vs. 61 ± 31, P = 0.04). A significant reduction of CECs and viable CECs was observed only in GBM patients with a clinical and radiological response after 2 months of therapy (111.6 ± 52.4 vs. 70.9 ± 55.3, P = 0.05 for CECs and 33.4 ± 18.3 vs. 16.2 ± 14.6, P = 0.03 for CECs viable). No significant difference in CEPs number and viability among patients and during treatment was detected. The data suggest that investigations of CEC investigation levels could contribute to a better understanding of clinical responses to bevacizumab action in HGG patients.

P.075*. THE EXPRESSION OF NG2 IDENTIFIES A TUMOR-COMPETENT POPULATION IN GLIOBLASTOMA WITH DISTINCT MOLECULAR SIGNATURE
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INTRODUCTION: We previously demonstrated that NG2 expressing (NG2+) cells in glioblastoma (GBM) exhibit robust proliferative and tumorigenic activity and share phenotypic and functional similarities with NG2 expressing glial progenitors. Here, we conducted comparative studies to address the difference of the molecular signature of GBM-NG2+ and GBM-NG2– cells. METHODS: ACGC2, an immortalized human astrocyte cell line, was used to generate NG2 expressing GBM-like cell lines. Gene Ontology enrichment identified more than 200 gene categories that were enriched in the GBM-NG2+ cells. The top 10 categories were related to cell cycling, M phase, and DNA replication. Similarly, CGH demonstrated subtle structural differences between the molecular cytogenetic profile of GBM-NG2+ and GBM-NG2–. Finally, we demonstrated that MAPK and Akt pathways were significantly overactivated in GBM-NG2+ compared with GBM-NG2– cells. CONCLUSION: We previously showed the robust proliferative activity and tumorigenicity of GBM-NG2+ cells. Here, we provide evidence that our previous observations are linked to the distinct molecular signature of GBM-NG2+ cells. This signature includes notable structural chromosomal abnormalities, unique enrichment of TFs and genes, and overactivation of MAPK and Akt pathways.

P.076*. NEOADJUVANT TEMOZOLOMIDE FOR GRADE III AND IV ATROCYTOMA: A RANDOMIZED PHASE II STUDY
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BACKGROUND: A pilot study conducted with TMZ given neoadjuvant before radiotherapy (RT) for astrocytoma grade III and IV resulted in long survival times compared with historical controls. We therefore further investigated the value of neoadjuvant TMZ in a randomized phase II trial. During the enrollment period, concurrent radiochemotherapy became standard treatment and was therefore incorporated in the later part of the trial. MATERIAL AND METHODS: Newly diagnosed patients with astrocytoma grade III (glioblastoma, GBM) or grade III (anaplastic astrocytoma, AA) age >60 years and performance status (PS) 0–2 were randomized to receive either 2–3 cycles of TMZ, 200 mg/m2 Days 1–5 every 28 days, followed by RT 60 Gy in 30 fractions or RT only. The third TMZ cycle was administered to patients with nonprogressive disease after 2 cycles of TMZ. From June 2005, all patients received TMZ 75 mg/m2 daily concomitant with RT. No adjuvant TMZ was given, but was recommended as first-line treatment at progression, unless patients progressed while on TMZ therapy. Primary endpoint

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was overall survival and secondary endpoints were safety and quality of life. RESULTS: A total of 143 patients were enrolled in the trial. Of these 87 (61%) received TMZ concomitant with RT. GBM was diagnosed in 103 patients and AA in 40. Median age was 58 years (range 24–60) and 63% were male. PS was 0–1 for 93.1% of patients and 87% had undergone surgical resection. The treatment arms were well balanced. Of all patients, 71 (50%) were randomized to the neoadjuvant treatment. Of these, 67 (94%) received the first cycle of TMZ, 64 (90%) the second, and 58 (82%) also the third. At the time of data analysis, 98 patients (68.5%) were dead. Median survival time for all patients was calculated to 20.5 months. CONCLUSIONS: The role of TMZ in the treatment of GBM given concomitant with RT and adjuvant is well documented. We explored the value of TMZ given neoadjuvant for 2–3 cycles, before RT for GBM and AA in a phase II randomized trial. The final results will be presented at the upcoming EANO meeting.

P.077* CANCER STEM CELLS IN Glioblastoma, WHAT ARE THEY? A. Golebiewska1, N. H. Brons2, R. Bjerkvig1,3, and S. P. Niclou1; 1Norlux Neuro-Oncology Laboratory, Public Research Centre for Health (CRP-Santé), Luxembourg, Luxembourg; 2Core Facility Flow Cytometry, Neuro-Oncology Laboratory, Public Research Centre for Health (CRP-Santé), Luxembourg, Luxembourg; 3Norlux Neuro-Oncology Laboratory, Department of Biomedicine, University of Bergen, Bergen, Norway

Glioblastoma multiforme (GBM) is one of the most heterogeneous tumors, both at the genetic and the cell morphology level. It has been proposed that only a subset of cancer cells display stem cell properties and are tumorigenic in vivo (cancer stem cells, CSCs). However, there is now growing evidence that expression of a putative stem cell marker, such as CD133, cannot define the only GBM subpopulation with tumor initiating capability. A number of studies have also shown that tumor initiation depends on the microenvironment and the animal model used, rather than being an intrinsic property of a subpopulation of tumor cells. In this project, we aim to characterize subpopulations of tumor cells with stem cell characteristics from GBM xenografts and determine whether these cells are a subpopulation of the tumor (bona fide CSCs) or represent a changing entity adapting to the signals from the microenvironment. To address this question we apply flow cytometry to identify and characterize small subpopulations of cells within a highly heterogeneous tumor population, according to cell surface and internal markers and according to their drug efflux properties (side population). We have set up an immunodeficient GFP expressing mouse xenograft model, which recapitulates the invasive and angiogenic features of human GBM. The use of a GFP mouse allows to distinguish between tumor and host cells, an important aspect since the invasive and angiogenic features of human GBM. As such, our data provide compelling evidence that CSCs are a novel entity involved in the cause of astrocytomas, with tumor suppressive and long-term progression acting factor roles.

P.078 SMALL MOLECULE KINASE INHIBITORS IN Glioblastoma: A SYSTEMATIC REVIEW OF CLINICAL STUDIES P. C. De Witt Hamer; VU Medical Center, Amsterdam, the Netherlands

The efficacy of small molecule kinase inhibitors has recently changed standard clinical practice for several solid cancers. Glioblastoma is a solid cancer that universally recurs and unrelentingly results in death despite maximal surgery and radiotherapy with concomitant and adjuvant temozolomide. Several clinical studies using kinase inhibitors in glioblastoma have been reported. The present study systematically reviews the efficacy, toxicity, and tissue analysis of small molecule kinase inhibitors in adult patients with glioblastoma as reported in published clinical studies and determines which kinases have been targeted by the inhibitors used in these studies. Publications were retrieved using a MEDLINE search and by screening of meeting abstracts. A total of 60 studies qualified for inclusion, 25 of which are first cycle report. A total of 2385 glioblastoma patients receiving kinase inhibitors could be evaluated. The study designs include 2 phase III and 37 phase II studies. Extracted data include radiological response, progression-free survival, overall survival, toxicity, and biomarker analysis. The main findings are (i) that efficacy of small molecule kinase inhibitors in clinical studies with glioblastoma patients does so far not warrant a change in standard clinical practice and (ii) that 6 main kinase targets for inhibitors have been evaluated in these studies (ie, EGFR, mTOR, KDR, FLT1, PKCa, and PDGFR).

P.079 NPAS3 IS A NOVEL LATE-STAGE ACTING PROGRESSION FACTOR IN GLIOBLASTOMA WITH TUMOR SUPPRESSIVE FUNCTIONS N. Ajewung1, M. Rana1, P. Gould2, and D. Kamnasaran1; 1Department of Pediatrics, Centre de Recherche du CHUL & Laval University, Quebec, QC, Canada; 2Department of Pathology, Laval University, Quebec, QC, Canada

BACKGROUND: In our effort to better comprehend the genetics of gliomas, we explored new therapeutic targets. We previously cloned NPAS3, a transcription factor that maps to human chromosome 14. Our principal aim is to comprehend the disease associations of NPAS3, since we recently identified expression in human astrocytes. We investigated NPAS3 as a candidate for astrocytomas based on findings archived from the Cancer Genome Project demonstrating a loss of NPAS3 expression and with loss-of-function deletions of human chromosome 14 with NPAS3 in 30%–50% of astrocytomas. METHODS AND RESULTS: After undertaking extensive functional analyses, we now have novel evidence supporting NPAS3 as an astrocytoma tumor suppressor involved in late-stage tumor progression, based on: (i) Absent NPAS3 expression is predominant in high-grade astrocytomas (79–83%), in comparison with low-grade astrocytomas (29–35%). (ii) Loss of function mutations of NPAS3, which are associated with a loss of heterozygosity of the NPAS3 locus, are identified in GBMs. (iii) Absent NPAS3 expression is predominant in >60% of malignant human glioma cell lines. (iv) An over-expressed NPAS3 in malignant glioma cell lines suppresses the transformation potential, while the converse reduced expression promotes an increase in transformation potential. (v) A reduced NPAS3 expression (efficiency >90%) in concert with other glioma genes can transform a well-characterized TERT immortalized human astrocyte cell line and promote the growth of anaplastic astrocytomas. CONCLUSION: Our data provide compelling evidence that NPAS3 is a novel gene involved in the cause of astrocytomas, with tumor suppressive and late-stage acting progression factor roles.

P.080 A NOVEL METHOD TO ENRICH FOR GLIOMA STEM CELLS FROM GLIOMA CELL LINES N. Ajewung, M. Rana, and D. Kamnasaran; Department of Pediatrics, Centre de Recherche du CHUL & Laval University, Quebec, QC, Canada

BACKGROUND: Glioma stem cells (GSCs) are inherently similar to stem cells except they can transform into tumors reminiscent of the pathological features of the originated tumor mass. GSCs serve as an excellent pre-clinical model to comprehend tumor re-growth and treatment resistance. Several approaches were previously described to purify GSCs, but seemingly appeared to be laborious, costly, and sometimes with poor yield. Our objective was to investigate alternative strategies to cost-effectively and efficiently enrich for GSCs. METHODS AND RESULTS: We grew 3 glioma cell lines in a monolayer serum-free medium or in growth of spheres over a 10-day period and with ease of harvesting from the supernatant. The tumorspheres had cell line-specific morphologies. For instance, those from U87 and DB5MG were significantly larger with tightly associated spheres, in comparison with those from U251. The tumorspheres expressed stem cell markers and in fact were 80%–96% rich in CD133+ve cells. Upon growth in DMEM/10% FCS, tumorsphere differentiation occurred. In addition, the tumorspheres can transform in vitro and within the ability to grow into tumors having similar pathological hallmarks but faster growth in comparison with xenograft tumors derived from the growth of glioma cell lines. These findings were overall similar with passages 1, 10, and 30 GSCs examined. CONCLUSIONS: We have discovered an alternative strategy to enrich for glioma stem cells from glioma cell lines in a cost-effective, easy, and efficient manner. Current efforts are undertaken to utilize our protocol to enrich for glioma stem cells from surgical tissues.

P.081 A CHEMICAL GENETICS SCREEN IDENTIFIES NOVEL STEROID INHIBITOR DRUGS THAT INHIBIT THE GROWTH OF GLIOMA CELL LINES N. Ajewung1, M. Rana2, D. Poirier2, and D. Kamnasaran1; 1Department of Pediatrics, Centre de Recherche du CHUL & Laval University, Quebec, QC, Canada; 2Laboratory of Medicinal Chemistry, Oncology and Molecular Endocrinology, Centre de recherche du CHUL & Laval University, Quebec, QC, Canada

BACKGROUND: Gliomas are among the top 5 causes of cancer-related deaths, representing about ~60% of the cases in adults and ~30% in children. Despite current treatments (surgery, radiation, and chemotherapy), the
overall survival is still poor. Current promises exist with patients treated with adjuvant temozolomide; however, only 10%–15% typically have a positive response with combined surgery and radiation therapies leading to prolonged survival of up to 2 years. Since a wide range of steroid receptors are expressed in gliomas, our objective was to investigate whether novel classes of steroid inhibitor drugs can be used efficiently to inhibit glioma growth. To achieve this, we studied the effect of these drugs on the growth of glioma stem cells.

METHODS AND RESULTS: We screened using a candidate chemical structure approach, a library of 400 steroid inhibitor drugs on 5 human glioma stem cell lines, and a normal human astrocyte cell line. We discovered 5 potent new steroid inhibitor drugs belonging to the methyl-piperazine family, which can induce significant death of glioma stem cells (n = 5/5) within a 24-hour period and, with some death of normal human neuro-progenitor cells. These drugs induced significant apoptosis, resulting in an overall decreased viability and proliferation of the cells in a dose-dependent manner (5 and 10 μM). Furthermore, significant inhibition of transformation was noted. CONCLUSIONS: We have discovered a novel chemically distinct class of drugs that can significantly inhibit the growth of glioma stem cells. Current efforts are undertaken to study more of the mechanistic function of these drugs.

P.082. A CHEMICAL GENETICS SCREEN IDENTIFIES NOVEL STEROID INHIBITOR DRUGS THAT INHIBIT THE GROWTH OF GLIOMA STEM CELLS
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BACKGROUND: Glioma stem cells represent a fraction of cells within a tumor mass that are postulated to be responsible for tumor re-growth. Moreover, recent studies have associated glioma stem cells with impeccable chemoresistance mechanisms, leading to an overall poor survival and failure among patients treated by conventional adjuvant chemotherapy. Since a wide range of steroid receptors are expressed in gliomas, our objective was to investigate whether novel classes of steroid inhibitor drugs can be used efficiently to inhibit glioma growth. To achieve this, we studied the effect of these drugs on the growth of glioma stem cells.

METHODS AND RESULTS: We screened using a candidate chemical structure approach, a library of 400 steroid inhibitor drugs on 5 human glioma stem cell lines established from surgeries (n = 2) and cell lines (n = 3), and a normal human neuro-progenitor cell line. We discovered 5 potent new steroid inhibitor drugs belonging to the methyl-piperazine family, which can induce significant death of glioma stem cells (n = 5/5) within a 24-hour period, and with some death of normal human neuro-progenitor cells. These drugs induced significant apoptosis, resulting in an overall decreased viability and proliferation of the cells in a dose-dependent manner (5 and 10 μM). Furthermore, significant inhibition of transformation was noted. CONCLUSIONS: We have discovered a novel chemically distinct class of drugs that can significantly inhibit the growth of glioma stem cells. Current efforts are undertaken to study more of the mechanistic function of these drugs.

P.083. BRAINSTEM GLIOMA IN ADULTS: A RETROSPECTIVE STUDY
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INTRODUCTION: Brainstem glioma are rare in adults. Literature on the subject is limited to small retrospective studies that described natural course, clinical-radiological presentation, and prognostic factors. Need for histopathological confirmation and therapeutic planning remains controversial. Surgery is first choice when tumor site permits it, even when only subtotal resection can be reached. Nevertheless, radiotherapy is very useful when tumor resection fails. We screened using a candidate chemical structure approach, a library of 400 steroid inhibitor drugs on 5 human glioma stem cell lines established from surgeries (n = 2) and cell lines (n = 3), and a normal human neuro-progenitor cell line. We discovered 5 potent new steroid inhibitor drugs belonging to the methyl-piperazine family, which can induce significant death of glioma stem cells (n = 5/5) within a 24-hour period, and with some death of normal human neuro-progenitor cells. These drugs induced significant apoptosis, resulting in an overall decreased viability and proliferation of the cells in a dose-dependent manner (5 and 10 μM). Furthermore, significant inhibition of transformation was noted. CONCLUSIONS: We have discovered a novel chemically distinct class of drugs that can significantly inhibit the growth of glioma stem cells. Current efforts are undertaken to study more of the mechanistic function of these drugs.

P.084. GAMMA-KNIFE RADIOSURGERY FOR RECURRENT GliOBlastoma Resistance TO THE TEMOZOMOLIDE K. Satou; Nakamura Memorial Hospital, Sapporo, Japan

PURPOSE: The current standard of care for newly diagnosed glioblastoma is surgical resection to the extent feasible, followed by radiotherapy plus concomitant and adjuvant temozolomide. Ultimately, despite this current standard treatment, almost all patients with glioblastoma will have relapse. Gamma knife radiosurgery (GK) radiosurgery is a safe and less invasive treatment used as adjuvant therapy for patients with glioblastoma. Several studies have yielded conflicting results in the effectiveness of radiosurgery in glioblastoma. This article describes the results of our institutional experience with GK adjuvant therapy in the treatment of patients with recurrent glioblastoma resistance to the temozolomide. METHODS: Eighteen patients with newly diagnosed glioblastoma were treated with operation and concomitant temozolomide radiochemotherapy from 2006 to 2009. Six patients with recurrent glioblastoma were treated for 26 lesions with GK. Two patients were male and 4 were female. The median age at primary diagnosis of the tumor was 65.5 years (range: 53–81 years). All patients were received debulking surgery. Histological evaluations of all patients revealed glioblastoma. In all patients, radiotherapy was performed as first-line therapy, applied as fractionated external beam radiotherapy with concomitant temozolomide chemotherapy. The median interval between initial diagnosis and primary treatment was 9.2 months (range: 6–11 months). The median target tumor size was 8.1 cm3 (range: 0.65–38.3 cm3). The median dose applied was 54 Gy (range: 15–20 Gy) prescribed to the 50% (range: 45%–80%) isodose line that encompassed the target volume. The median follow-up time was 22.5 months (range: 14–37 months). RESULTS: Median survival time of patients treated with GK was 19.0 months and without GK was 15.0 months. Treatment was well tolerated by all patients. No acute toxicities CTCAE Grade II occurred. Median survival time of patients treated with GK was 19.0 months and without GK was 15.0 months. CONCLUSIONS: GK radiosurgery is a relative safe and less invasive treatment and may play an important role in the treatment of recurrent glioblastoma resistance to the temozolomide.

P.085. DOES GENDER MATTER IN GliOBlastoma? E. Verger, I. Valdeneivo, L. Caral, T. Pujol, T. Ribaltà, N. Vínolas, T. Boget, L. Olega, Y. Blanco, and F. Graus; Hospital Clinic, Barcelona, Spain

BACKGROUND: Clinical outcome of glioblastoma (GBM) patients who receive radiotherapy alone or plus chemotherapy is well established. However, little is known about patients who do not receive this treatment. In published studies, it is difficult to identify the percentage of patients who never receive oncological treatment after surgery and to determine the associated variables. METHODS: We reviewed all GBM patients operated in our hospital between January 2000 and December 2008. Patients’ clinical data at our center are prospectively included in a database. We compare those who received oncological treatment and those who did not.

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Variables analyzed were age, gender, clinical presentation, pre- and post-surgery KPS, size, location, extent of surgery, and surgical complications. RESULTS: A total of 216 patients with GBM were identified. Fifty-five (25%) did not receive any treatment after surgery. Univariate analysis showed that variables associated with the absence of oncological treatment were: gender, 33% women vs 20% of men were not treated, P = 0.03; age, median age 36 years (treatment) vs 64 years (no treatment), P = 0.001; initial KPS of patients with KPS ≤ 60 vs 18% of those with KPS > 60 were not treated, P ≤ 0.0001; and post-surgery KPS, 68.3% of patients with KPS ≤ 60 vs 8% of those with KPS > 60 were not treated, P = 0.0001. In the multivariate analysis age (> 60 vs ≤ 60, OR = 2.5, 95% CI: 1.1–5.7, P = 0.02) and post-surgery KPS (KPS ≤ 60 vs > 60, OR = 24.7, 96% CI: 11.0–55.5, P = 0.0001) were independent predictors of no treatment after surgery. We analyzed why there were more women in the non-treatment group. Women in the whole series were older than 60 years, P = 0.01, they had a worse KPS before, P = 0.04, and after surgery, P = 0.02, and had more biomarkers, P = 0.04. In the multivariate analysis, gender was associated with a lower pre-surgery KPS (women vs men, OR = 2.7, 95% CI: 1.2–6.1, P = 0.014) and older age (> 60 vs ≤ 60, OR = 2.0, 95% CI: 1.2–3.5, P = 0.013) at diagnosis. In the whole group, median survival time (MST) was 315 days for men (n = 125) vs 216 days for women (n = 91), log rank P = 0.03. However, in the treated group, we did not observe any difference in MST between men and women. CONCLUSIONS: One out of the 4 patients could not be treated after surgery. Associated factors were older age and lower KPS. These poor risk variables were more frequent in women, and they therefore had a lower survival in our series.

P.086. RECURRENT SPINAL CORD GliOBlastoma SALVAGE THERAPY WITH BEVACIZUMAB
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BACKGROUND: Primary spinal cord tumors constitute 2%-4% of all primary CNS malignancies in adults of which less than 5% are glioblastoma. A retrospective evaluation to determine toxicity and response to bevacizumab in patients with recurrent spinal cord glioblastoma. PATIENTS AND METHODS: 36 patients were treated (18 males and 18 females; median age 43, range 21-79) with recurrent spinal cord glioblastoma were treated with bevacizumab (10 mg/kg given once every 2 weeks where treatments constituted a cycle of therapy). All patients had failed surgery and temozolomide-based chemoradiation and post-radiotherapy temozolomide. Blood counts, chemistry panel, urine protein to creatinine ration, and neurologic examination were obtained bi-weekly. Contrast-enhanced spine MRI was performed after 1 cycle of therapy and thereafter following every 2 cycles of bevacizumab. RESULTS: Treatment-related complications included fatigue in 6 patients, constipation in 4, hypertension in 2, thrombophlebitis in 2, and infection without neutropenia in 2. There were 3 grade 3 toxicities (1 each, fatigue, leukopenia, and thrombophlebitis). There were no treatment-related deaths. After one cycle of bevacizumab, 1 patient (17%) demonstrated progressive disease, 2 (34%) partial responses, and 3 (51%) stable disease. Overall median response or stable disease duration (disease free progression) was 7 months (range: 3–11 months). Overall median survival was 9 months (range: 5–13 months). CONCLUSIONS: Bevacizumab is well tolerated, has tolerable toxicity, and apparent activity in this small cohort of adults with recurrent spinal cord glioblastoma.

P.087. CONCURRENT 3-TIMES DAILY ULTRAFACTIONATED RADIATION THERAPY AND TEMOZOLOMIDE FOR NEWLY INOPERABLE GliOBlastoma: TEMoFRAC, A PHASE II STUDY
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BACKGROUND: Ultrafractionation radiotherapy causes in irradiating cells or tumors several times daily, delivering low doses at which hyperra- diosensitivity occur. We have conducting a phase II clinical trial to determine the effect of a concurrent ultrafractionation regimen and temozolomide for inoperable glioblastoma patients. METHODS: A phase II study has opened for accrual in February 2008. Patients over 18 years of age who are able to give informed consent and have histologically proven, newly inoperable diagnosed and supratentorial glioblastoma are eligible. Three doses of 0.75 Gy spaced by at least 4 hours are delivered daily, 5 days a week for 6 consecutive weeks (67.5 Gy), and concomitant chemotherapy consisted of temozolomide given 7 days per week during the ultrafractionated radiotherapy. After a 4-week break, chemotherapy is resumed up to 6 cycles. An adjuvant temozolomide was given every 28 days. Tolerance and toxicity are the primary endpoints and survival and progression-free survival are the secondary endpoints. RESULTS: To date, 31 patients have been enrolled in this study, 21 men and 10 women, median age 62, median Karnofsky performance status was 80. The concurrent ultrafractionated radiotherapy–temozolomide, has been well tolerated; no acute grade 3 and/or 4 CNS toxicity has been observed and 1 grade 4 hematological toxicity was reported during the combined therapy. Two patients progressed during the radiotherapy, and 2 patients died of pulmonary embolism. Median survival was not yet reached. CONCLUSIONS: Concurrent ultrafractionated radiation (temozolomide) is safe and well tolerated. At meeting, an analysis of survival will be given.

P.088. CONCURRENT RADIOTHERAPY–FOTEMUSTINE COMBINATION FOR NEWLY MALIGNANT GLIOMA PATIENTS: A PHASE II TRIAL
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PURPOSE: Fotemustine is a nitrosourea compound used for the treatment of malignant gliomas, especially in France. Recently, an EORTC-NCIC study has shown that a concomitant combination of radiotherapy plus temozolomide (an oral cytotoxic drug) improved survival in glioblastoma patients. We set out to test a concurrent combination of radiotherapy and fotemustine for newly malignant gliomas. METHODS: A prospective single-centre phase II study opened for accrual in September 2004. Patients over 18 years of age able to give informed consent and with histological proven, newly diagnosed supratentorial malignant gliomas were eligible. All patients were treated by a standard cranial irradiation (conformal irradiation, tumor bulk plus a margin of 2.5 cm) and concomitant daily administration of 10 mg/m2 of fotemustine (5 days per week, 6 weeks, 1 hour 30 minutes before radiotherapy). Adjuvant chemotherapy, fotemustine, was administered at tumor progression as standard and classic regimen. RESULTS: Twenty-two patients were enrolled, 16 men and 6 women, median age 56 years (range: 32–74 years), median Karnofsky performance status 70 (range from 60 to 90). Histology included 16 glioblastomas, 3 anaplastic astrocytomas, 2 anaplastic oligodendrogliomas, and 1 mixed glioma. Eight patients underwent surgery (3 total resections) and 14 had a stereotactic biopsy. The concurrent radiotherapy–fotemustine combination was well tolerated: toxicity was mild and 3 hematologic toxicities grade 3–4 were observed. Median survival from initial diagnosis was 9.9 months, 2 patients are currently alive. Median survival was 11 months for surgery and 9 months for stereotactic biopsy. CONCLUSIONS: Concomitant radiotherapy–fotemustine combination is safe and well tolerated. Overall survival of over 10 months for the whole population compares favorably with other reports.

P.089. GENE EXPRESSION PROFILING PREDICTS RESPONSE TO TMZ IN GliOBlastOMAS IN VITRO
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Glioblastomas are highly lethal neoplasms that cannot be cured which currently available therapies. Temozolomide (TMZ) is a recently introduced alkylating agent that has yielded significant benefits and become a key agent in the treatment of high grade gliomas including glioblastoma. However, its survival benefit remains unsatisfactory. Understanding the molecular basis of TMZ sensitivity/resistance is necessary for improving the treatment outcome by devising strategies that are able to circumvent primary drug resistance. We therefore combined the in vitro TMZ response with microarray expression data to identify genes that could potentially be used to predict the response of glioblastomas to
P.090. TEMOZOLOMIDE DOSE DENSE AS SALVAGE TREATMENT FOR GLOBLASTOMA
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BACKGROUND: There is no clear agreement for the choice of the best second-line regimen after failure of temozolomide standard schedule (TMZ-SS) in patients with recurrent glioblastoma (GBM). In patients with relapsed GBM, dose-dense regimens of TMZ (TMZ-DD) have been applied and the weekly alternating showed low toxicity and good efficacy. METHODS: We have retrospectively analyzed clinical data of 14 patients treated with TMZ-DD 150 mg/m2 5 day every week after failure with TMZ-SS in patients with primary GBM. RESULTS: Between July 2007 and January 2010, 14 patients (9 men and 5 women; median age 56; range: 36–72) followed at our institution for primary GBM underwent TMZ-DD. Eight patients (57%) for progression after second surgery. Six patients showed a complete response (CR) and stable disease (5 patients), with a median duration of 14.3% for progression after second surgery. Six patients showed a complete response (CR) and stable disease (5 patients), with a median duration of

P.091. HYPOFRACTIONATED HIGH-DOSE IRRADIATION PLANNED BY METHIONINE PET FOR THE TREATMENT OF GLOBLASTOMA MULTIFORME
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PURPOSE: The ability of intensity modulated radiation therapy (IMRT) to deliver a high conformative dose of irradiation to the target has promoted its application studies for patients with glioblastoma multiforme (GBM). Generally, the dose-escalation efforts have relied on the contrast-enhanced MRI, although contrast enhancement is not always an accurate measure of tumor extension. Metabolic imaging studies such as 1H-methionine PET (MET-PET) may improve the ability to identify the target volumes at highest risk of local failure. In this study, we evaluated the clinical significance of hypofractionated high-dose irradiation planned by MET-PET with MRI and confirmed by MET-PET. MATERIALS AND METHODS: Thirty-nine postoperative patients with GBM were treated by IMRT using the tomotherapy system with concurrent chemotherapy. The gross target volumes by MRI (GTV-MRI) were defined as the residual gross tumor or resection cavity, based on the contrast-enhancement MRI. The CTV-MRI was expanded uniformly by 1.5 cm to form the MRI clinical target volumes (CTV-MRI). GTV-MET was considered to be that the area of intense MET uptake, demonstrating a threshold of 1.7 for the standardized uptake value (SUV) of the tumor, compared with that of the normal brain. CTV-MET was considered to be that the area of moderate MET uptake, demonstrating a threshold of 1.3 for the SUV. GTV was finally defined as the area including the total volume of GTV-MRI and GTV-MET, and CTV was defined as the area including the total volume of CTV-MRI and CTV-MET. The GTV and CTV were expanded uniformly by 0.5 and 0.2 cm to generate planning target volumes, PTV-1 and PTV-2, respectively. IMRT was performed in 8 fractions, planning the dose for PTV-1 at 56 Gy and PTV-2 at 40 Gy with concurrent chemotherapy by temozolomide (TMZ) of 75 mg/m2 daily. Adjuvant chemotherapy by TMZ of 150 mg/m2 was repeated every 4 weeks. At a median follow-up of 13 months, the treatment outcomes and toxicity were evaluated. RESULTS: The median survival time was 18.5 months. The 1- and 2-year progression-free survival rates were 59% and 20%, respectively. The 1- and 2-year overall survival rates were 74% and 24%, respectively. The high incidence of CSF dissemination was demonstrated as the pattern of recurrence, while the incidence of local recurrence was relatively low. Five patients experienced acute grade 1 toxicity during the treatment. Nine patients experienced grade 2 toxicity, including radiation necrosis, cerebroepithelial, and intratumoral hemorrhage. CONCLUSIONS: Our regimen of IMRT with TMZ using MET-PET contributed to the control of residual infiltrating tumor, resulting in better survival of GBM patients. Survival times in this pilot study are encouraging, and relative favorable result might be from the decreasing of local failure, which suggested that original lesion could be well controlled by high-dose radiation planned by MET-PET. On the other hand, radiation-induced late toxicity was the next problem.

P.092. EFFICACY AND TOLERABILITY OF LEVETIRACETAM MONOTHERAPY IN PATIENTS WITH PRIMARY BRAIN TUMORS AND EPILEPSY
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OBJECTIVES: Epilepsy is a common symptom in patients with brain tumors, particularly gliomas. Enzyme-inducing or -inhibiting antiepileptic drugs (AEDs) are known to interact with antineoplastic drugs and corticosteroids, resulting in altered drug levels and potential ineffectiveness or toxicity. Levetiracetam does not have these interactions and may benefit these patients. We aimed to determine the efficacy and tolerability of levetiracetam monotherapy in glioma patients with epilepsy. METHODS: Forty glioma patients with epilepsy were recruited. All patients had undergone surgery and were on levetiracetam monotherapy at the time of inclusion. They were included within 6 weeks postoperatively. Treatment with levetiracetam was continuing to the routine care of patients with glioma, adding additional characteristics regarding patient, tumor, and epilepsy history were documented. Follow-up took place after 3 and 6 months. Seizure reduction (compared with preoperative baseline) and drug withdrawal as a result of adverse effects or tumor progression were defined as the primary outcome. RESULTS: Three patients died during follow-up: all 3 because tumor progression. After 6 months, 21 patients (57%) were seizure-free, whereas 6 patients (16%) reported a reduction in seizure frequency of >50% and 2 patients (5%) reported no change. Ability to maintain seizures frequency were encouraging. Seven patients (18%) had to switch to another AED because of lack of efficacy (n = 4) or adverse effects (n = 3). Efficacy was not related to any clinical characteristic. CONCLUSIONS: Although earlier studies indicate that add-on therapy with levetiracetam seems effective, there is hardly
any information available on levetiracetam monotherapy. Our results indicate that levetiracetam monotherapy is efficacious in reducing seizures and is well tolerated in the majority of glioma patients suffering from epilepsy.

P.093. AGGRESSIVE TREATMENT IS APPROPRIATE FOR ELDERLY (70 YEARS AND OLDER) PATIENTS WITH GlioBLASTOMA MultiFORME: A RETROSPECTIVE REVIEW OF 206 CASES

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PURPOSE/OBJECTIVE(S): Elderly patients have largely been excluded from large, randomized trials of therapy for glioblastoma multiforme (GBM). Small randomized trials have been done, evaluating the effect of individual treatment modalities. We reviewed our results of aggressive treatment with chemotherapy, radiation, and resection in this group of patients. PATIENTS AND METHODS: From an IRB-approved institutional brain tumor database, we identified patients 70 years of age and older who were newly diagnosed with GBM from May 1979 through September 2007. KPS (P = 0.001), age at diagnosis, median OS was 4.5 months. In univariate analysis, factors that significantly affected OS included Karnofsky performance status (KPS) (1.8 months for KPS ≤ 50 vs 17.2 months for KPS ≥ 90, P < .001), age at diagnosis (5.1 months for age 70–79 vs 3.1 months for age 80 or greater, P < .001), the extent of disease with patients with bilateral disease (P = .003), multifocal disease (P = .02), and multicentric disease (P = .002) doing worse in all cases. Patients treated with radiation had longer survival than those not treated with radiation (P < .001). As did patients treated with chemotherapy who had an OS of 11.2 vs 3.5 months compared with the 80-μM trabedersen group and the highest tumor control rate (CR + PR + SD) at 14 months (22.5% for 10 μM trabedersen vs 6.7% for chemotherapy). The highest efficacy was observed in AA patients treated with 10 μM trabedersen; the proportion of patients showing a response (either CR, PR, or SD) in AA patients was 83% (10 of 12 patients) in the 10-μM trabedersen group, 53% (8 of 15 patients) in the 80-μM trabedersen group, and 58% (7 of 12 patients) in the chemotherapy group.

RESULTS: Two hundred and six patients 70 years of age and older were newly diagnosed with GBM from May 1979 through September 2007. The median time to progression was 22.4 months for the 10-μM trabedersen group and 13.0 months for the chemotherapy group. Furthermore, the 10-μM trabedersen group showed a 17.4-month median survival benefit of 17.4 months over chemotherapy (39.1 vs 21.7 months). In addition, promising efficacy data were observed in GBM, especially in patients with age ≤ 55 years and KPS ≥ 80. Trabedersen generally had a good tolerability and safety profile. CONCLUSIONS: Trabedersen treatment is a clear clinical benefit in GBM. On the basis of the phase IIb results, the pivotal phase III study SAPPHIRE in patients with recurrent/refractory AA was started. Patient recruitment is ongoing. Primary endpoint is 2-year survival; secondary endpoints include overall survival, tumor response, quality of life, and safety.

P.094. TRABEDERSEN IN RECURRENT HIGH-GRADe GLIOBLASTOMA: IMPACT ON TUMOR CONTROL AND SURVIVAL

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INTRODUCTION: TGF-β2 regulates key mechanisms of cancerogenesis, namely immunosuppression, metastasis, angiogenesis, and proliferation. The antisense oligonucleotide trabedersen (AP 12009) is a TGF-β2-specific inhibitor and is developed for the treatment of patients with highly malignant tumors such as recurrent or refractory high-grade glioma (HGG). METHODS: Clinical studies with trabedersen in HGG have included 3 phase I/II studies and 1 randomized, active-controlled, open-label, multicenter, dose-finding phase IIb study. These studies were performed in adult patients with recurrent or refractory HGG (AA, WHO grade II and GBM, WHO grade IV). Trabedersen was administered intratumorally by convection-enhanced delivery. RESULTS: In the phase IIb study, a total of 143 patients were randomized to either 1 of the 2 doses of trabedersen (10 or 80 μM) or to chemotherapy (TMZ or PCV). One hundred and thirty-four patients received study medication during a treatment period of about 6 months. In the entire study population, the 10-μM trabedersen group had the highest tumor control rate (CR + PR + SD) at 14 months (22.5% for 10 μM trabedersen vs 6.7% for chemotherapy). The highest efficacy was observed in AA patients treated with 10 μM trabedersen; the proportion of patients showing a response (either CR, PR, or SD) in AA patients was 83% (10 of 12 patients) in the 10-μM trabedersen group, 53% (8 of 15 patients) in the 80-μM trabedersen group, and 58% (7 of 12 patients) in the chemotherapy group. In addition, the duration of response was highest in the 10-μM trabedersen group with 29.1 months compared with the 80-μM trabedersen (24.0 months) and the chemotherapy group (8.0 months). The median time to progression was 22.4 months for the 10-μM trabedersen group and 13.0 months for the chemotherapy group. Furthermore, the 10-μM trabedersen group showed a 17.4-month median survival benefit of 17.4 months over chemotherapy (39.1 vs 21.7 months). In addition, promising efficacy data were observed in GBM, especially in patients with age ≤ 55 years and KPS ≥ 80. Trabedersen generally had a good tolerability and safety profile. CONCLUSIONS: Trabedersen treatment is a clear clinical benefit in GBM. On the basis of the phase IIb results, the pivotal phase III study SAPPHIRE in patients with recurrent/refractory AA was started. Patient recruitment is ongoing. Primary endpoint is 2-year survival; secondary endpoints include overall survival, tumor response, quality of life, and safety.

P.095. INCIDENCE AND SURVIVAL IN GlioBLASTOMA PATiENTS WITH PSEuDO-PROGRESSION IN A SiNGLE iNSTiTuTion

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We evaluate incidence and impact in survival and progression-free survival of pseudo-progression (PSP) in patients with glioblastoma (GBM). From December 2006 to September 2009, 61 primary GBM were treated in our institution with resection (54) or biopsy (7) followed by TMZ radiotherapy followed by TMZ (150–200 mg/m2/day for 5 days each 28) for 2 years or until disease progression or unacceptable toxicity. One month after chemoradiotherapy, MRI was performed and compared with the MRI done within 72 hours after surgery. The 12 and 24 months survival rate and PFS were analyzed by the Kaplan–Meier method, with the use of 2-sided log-rank test statistics. The median age was 57 years (range: 16–72), 43 were males. The median follow-up was 12 months (range: 2–37). The MRI 1 month after the end of radiotherapy showed progressive enhancement in 33 patients (57.3%) and stable disease or minor partial response in 26. All continued with 2 or 3 cycles of temozolomide. Of the 35 patients with progression in the postradiotherapy, MRI 14 (22.9%) had PSP and 21 (34.4%) real early progression (REP). Fifteen of 21 patients (71%) with REP developed new clinical symptoms during or 1 month after radiotherapy but only 4 of the 14 patients (28%) with PSP had new symptoms during this period. PFS was 57% and 21% at 12 and 24 months, respectively; the 12 and 24 months survival rate was 59% and 43%, respectively. There was a statistical significant difference in PFS in patients with PSP (P < .0013) and a trend toward better overall survival for patients with PSP but it did not reach statistical significance (P = 0.08). These data increase the notion to continue TMZ in the case of progressive lesions immediately after TMZ radiotherapy. Further research is needed to establish reliable imaging parameters that distinguish between REP and PSP.

P.096. SALVAGE THERAPY AFTER FAILURE OF FIRST LINE TREATMENT FOR GlioBLASTOMA MULTIforme

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Concomitant chemoradiotherapy is a mainstream of treatment for glioblastoma multiforme; however, all patients progress after the initial treatment. We analyzed treatment our patients received after the progression. Since the introduction of concomitant chemoradiotherapy in the year 2004, we treated 326 patients until the end of 2008. Of those 94 had radiologically demonstrated disease progression and were considered for second-line therapy. Their median age was 53 years (22–78, SD 12.3 years) and after discussion at MDT 39 patients were offered best supportive care, 3 patients were re-challenged with temozolomide, 17 had surgical resection followed by systemic therapy (either BCNU or PCV, 24 received BCNU chemotherapy, and 11 received other systemic therapy (either dose dense temozolomide or bevacizumab and irinotecan). Overall median survival was 16.6 (SD 1) weeks, in patients receiving best-supportive care it was 7.1 (SD 3.3) weeks, 13.5 weeks in patients re-challenged with temozolomide, 26.5 (SD 7.9) weeks in patients which were operated and later received systemic therapy,
P.097. THE USEFULNESS OF MS-MLPA FOR DETECTION OF MGMT PROMOTER METHYLATION IN THE EVALUATION OF PSEUDO-PROGRESSION IN GLIOBLASTOMA PATIENTS

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We investigated the usefulness of the methylation-specific multiplex ligation probe amplification (MS-MLPA) designed for evaluating semiquantitative O6-methylguanine DNA methyltransferase (MGMT) promoter methylation status to diagnose the pseudo-progression, which is a major diagnostic dilemma in modern treatment protocol involving concurrent chemoradiotherapy in malignant gliomas. Methylation ratio of promoters of MGMT and mismatch repair (MMR) genes and their copy number variation is assessed with MS-MLPA on 24 samples of glioblastoma patients. The results were comparably with those of methylation-specific polymerase chain reaction (MSP) and the protein expression of gene was confirmed by immunohistochemical (IHC) staining. Correlation between those molecular parameters and clinical outcome was analyzed. In case of radiological progression after chemoradiotherapy, the sensitivity and specificity of the MS-MLPA were 100% and 75% which was better than MSP in the decision of pseudo-progression using cut-off value of 0.2 for methylation ratio and 0.8 for copy number ratio. MS-MLPA result of MGMT gene was well correlated with those of MSP and IHC staining while there was insignificant correlation between MSP and IHC staining. MMR genes had little variability in promoter methylation and their protein had homogeneous tissue expression. We conclude that MS-MLPA is a useful method for the early detection of pseudo-progression in glioblastoma patients.

P.098. INTRAOPERATIVE TISSUE FLUORESCENCE USING 5-AMINOLEVOLINIC ACID (ALA) IS MORE SENSITIVE THAN CONTRAST-MRI OR AMINO ACID (FET)-PET GUIDED GLIOBLASTOMA (GBM) SURGERY

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OBJECTIVE: The ability of 5-ALA to visualize white matter infiltration zones of GBM with contrast MRI or [18F] fluorothethyltyrosine positron emission tomography (PET) was investigated. METHODS: Fluorescence tissue margins were mapped intraoperatively by neuronavigation and compared with pre- and postoperative MRI and FET–PET scans in 3 glioblastoma patients (2 temporal, 1 fronto-central tumor). RESULTS: In all patients, the intraoperatively detected 5 ALA fluorescence exceeded the MRI contrast tumor areas and FET–PET uptake, verified by intraoperative neuronavigation. Furthermore, all patients received complete resection of contrast affine tumor parts, which was verified by contrast MRI scans within 24 h of surgery. Additionally, intraoperative fluorescence tissue was generally left in place, because it was estimated as tissue at risk for neurological deterioration, no contrast affine tissue could be detected by postoperative MRI. Additionally, postoperative FET–PET uptake was demonstrated only in one patient as a small residual spot. FET–PET did not show any uptake at the intraoperatively mapped large marginal areas of 5 ALA fluorescence, left in place in account of neurological preservation. CONCLUSION: Our findings demonstrate that 5 ALA fluorescence is more sensitive than FET–PET and MRI contrast uptake in detecting glioblastoma multinode white matter infiltration zones.

P.099. EVALUATION OF ADVANCED MR TECHNIQUES FOR DEVELOPMENT OF EARLY BIOMARKERS FOR TREATMENT EFFICACY IN MALIGNANT BRAIN TUMORS

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BACKGROUND: Glioblastoma multiforme (GBM) is the most common group of brain tumors in adults with a median survival of only 1 year. A bottleneck in treatment evaluation is that changes in radiologic tumor size are a late effect. Hallmarks of malignant gliomas including tumor vascularity, high cell density, and heterogeneity can indirectly be measured using advanced MRI techniques, such as dynamic contrast enhancement (DCE), MRI, diffusion MRI, and MR spectroscopy (MRS). PATIENTS AND METHODS: Fifteen patients with GBM were included in the study: 10 patients obtaining first-line therapy (radiotherapy 2 Gy/60 Gy) concomitant with temozolomide (RT/Tmz) and 5 patients obtaining second-line therapy: temozolomide 125 mg/m2 concomitant with bevacizumab (Bvz) 10 mg/kg every 14 days, MR, diffusion MRI, and DCE–MRI were performed at baseline, day 1, 2 weeks, and 6 weeks after treatment start. All measurements were performed with a 1.5-T Siemens Espree. Calculations of apparent diffusion coefficient (ADC) maps were based on a SE–EPI sequence (b-values: 0 and 1000). CSI–MRS was performed using an echo-time of 135 ms, DCE–MRI measurements utilized a pharmacokinetic model to construct parametric maps for Vc and Vp. Regressions of Vc and Vp were performed at different time points were performed using the Insight registration and segmentation toolkit (ITK) implemented in a Matlab® environment. RESULTS AND DISCUSSION: In general, following observations were made: highly pronounced individual differences. MRS: In patients treated with RT/Tmz, there was a steady decrease of the Cho/NAA and the Cho/Chr ratio which persisted during the treatment period and was detected as early as 2 weeks after treatment start. The decline was more pronounced during the first 2 weeks than the rest of the 6-week period. DCE–MRI: An increase in mean ADC values could be visualized at day 1, and a gradual increase persisted during the 6-week follow-up. DCE–MRI: In patients treated with Bvz/Tmz a clear decrease in Ktrans could be seen after only 3 weeks of treatment with DCE–MRI, indicating a decrease of vascular permeability and leakage respectively. CONCLUSIONS: Important surrogate markers for angiogenesis, diffusion, and cell density tend to assume a more “normal” pattern after a very short treatment period in a series of patients. Studies with the objective to expand the number of patients and correlate these findings to patient outcome are ongoing at our department.
planning and preparation for treatment, and eligibility and entry for clinical trials and consent. Patients are offered as many appointments as they require.

DISCUSSION: Patients with brain tumors are being offered increasing options for treatment; however, the trauma of the diagnosis and the complexity of the discipline call for much greater communication with and planning from the treatment team. We have implemented a novel PTAC run primarily by nonmedical staff as an efficient and effective mechanism to respond to these demands. We plan to audit measures of effectiveness and satisfaction during a change-over period to demonstrate its value.

P.101. MALIGNANT GliOMA SURGERY IN ELOQUENT BRAIN AREAS
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OBJECTIVES: The surgical studies have demonstrated that the extent of anaplastic glioma resection is significantly correlated with patient median survival. Resection of brain tumors adjacent to eloquent areas remains a procedure with high-level postoperative neurological disorders as a result of wide tumor infiltration of functional cortex and subcortical pathways. Accurate preoperative and intraoperative identification of the eloquent cortex is an essential aspect of surgical excision. Methods: We studied 32 patients with gliomas involving motor and speech area. METHODS: A total of 36 patients (21 males, 15 females, mean age 48.3 years, range 21–70 years) who underwent resection of cortical or subcortical tumors located within or close to motor areas have been included in the study. The protocol of surgical excision was done using CT, MRI, fMRI, SPECT, and computed EEG studies. Brain tumors located in eloquent area in 21 patients (motor area in 12 cases, sensory area in 9 cases) and in close to eloquent area in 15 patients (motor area in 5 cases, sensory area in 7 cases). Tumor microsurgery resection was carried out using the StealthStation navigation system accompanied with intraoperative laser thermodestruction (808 nm, 18 W). RESULTS: Sixteen patients had glioblastoma multiforme and 20 had anaplastic astrocytoma. A gross total or nearly gross total tumor resection was accomplished in 19 patients, and subtotal resection was carried out in 17 patients. Neuronavigation technology helped to define the radiographic limits of the tumor, to perform preoperative planning and minimal access craniotomy. The intraoperative orientation by connection of anatomical and functional landmarks allowed performing image-guided tumor excision beyond functional zones with maximal extension of tumor resection volume. Laser thermodestruction of residual tumor parts was used after microsurgical tumor removal in regions around sensorimotor and speech areas. Laser thermodestruction increased the rate of complete citoreduction and performed an aimed coagulation without traumatization of eloquent cortex. CONCLUSIONS: The gross total resections of anaplastic gliomas could be performed in eloquent brain regions with an acceptable level of motor and speech impairment. The improved preoperative planning, mapping, intraoperative neuronavigation techniques, and laser thermodestruction allow maximal safe resection of tumor that predict higher levels of quality of life in patients with brain gliomas in eloquent area.

P.102. NEAR-CONTINUOUS TEMOZOLOMIDE AND LOW-DOSE WEEKLY CCNU: A NOVEL CHEMOTHERAPY REGIMEN WITH ACTIVITY IN MALIGNANT GLIOMAS RESISTANT TO DOSE-DENSE TEMOZOLOMIDE ALONE
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BACKGROUND: Alkylating chemotherapy with CCNU is active in recurrent malignant glioma, but may be antagonized by anti-alkylating MGMT. Here, we present feasibility and activity of a novel regimen aiming at depletion of MGMT with lower dose, near-continuous temozolomide followed by low-dose weekly CCNU to treat recurrent malignant gliomas resistant to dose-dense temozolomide. METHODS: Eleven consecutive patients with recurrent malignant gliomas (4 glioblastomas, 3 gliosarkomas, and 4 anaplastic gliomas) were treated: 6 males (55%), 5 females (45%); mean age at first diagnosis was 55.9 (19–76) years; median Karnofsky Performance Status 70%; 9 patients were treated for a second recurrence and 2 for first recurrence. All patients were pretreated with dose-dense temozolomide (day 1–21/28 or 1–5/7, initial dose 100 mg/m2). Nine of the 11 patients were switched without delay from dose-dense temozolomide monotherapy to combined near-continuous temozolomide (50–60 mg/m2 day 1/5/7) plus weekly low-dose CCNU (40 mg fix dose at day 6/7). RESULTS: In total, 32 cycles of chemotherapy were applied. The combination was well tolerated in terms of nausea and fatigue. Blood counts decreased continuously, enabling a gradual dose adaptation. Hematological WHO grade III + IV toxicity occurred in 5 of 11 patients (45%), 2 of them were symptomatic. One patient had a prolonged elevation of liver enzymes which improved partially after a second reevaluation of levotracetam. Best response after ≥2 months were: 1 complete and 2 partial remissions (27%), 3 stable diseases (27%), 5 progressive diseases (46%). Median overall survival after start of chemotherapy was 4.5 months, progression-free survival at 6 months (95% CI) was 18%, overall survival at diagnosis 23.5 months. CONCLUSIONS: In spite of adverse prognostic signs, the objective remissions indicate activity of combined near-continuous temozolomide and low-dose weekly CCNU after failure of dose-dense temozolomide alone. Hematotoxicity, though, has to be controlled vigorously. The results have to be controlled in a larger, prospective series.

P.103. RADIONUCLIDE PLUS CONCOMITANT AND ADJUVANT TEMOZOLOMIDE FOR GliOBLASTOMA IN ELDERLY PATIENTS
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OBJECTIVES: The optimal treatment for elderly patient with glioblastoma remains controversial. The aim of this study was to verify the activity and the toxicity of temozolomide (TMZ) administration concurrent and adjuvant to radiotherapy in elderly patients with glioblastoma (GBM), and to explore correlation between clinical outcome and (6)-methylguanine-DNA-methyltransferase (MGMT) promoter methylation status. METHODS AND PATIENTS: From April 2006, 23 consecutive newly diagnosed GBM patients aged 65 years or more (median age 72 years) and a KPS of ≥50 were treated with radical radiotherapy (45 Gy for all patients and 40 Gy for 7 patients) plus continuous daily TMZ (75 mg/m2/day), followed by maintenance TMZ cycles (200 mg/m2 once a day for 5 consecutive days every 28 days) until complete response or unequivocal progression. RESULTS: The median OS was 13.7 months and median PFS was 8.3 months. The 6- and 12-month survival rates were 79% and 61%, respectively. The 6- and 12-month PFS rates were 54% and 40%, respectively. Four patients had grade III neuroepithelioma and 1 patient had grade III thymoblastoma and 11 patients had grade III/IV lymphoblastoma. Two patients had grade III infection resolved with medical therapy. Leukoencephalopathy was diagnosed in 2 patients who survived more than 12 months. This was associated with memory loss in 1 patient. The methylation status of the MGMT promoter was evaluated in 23 patient samples. The median OS was 25.8 months vs 9.0 months in patients with MGMT promoter methylated status and with unmethylated MGMT promoter status, respectively (P = .03). CONCLUSIONS: Radiotherapy plus concomitant and adjuvant TMZ was well tolerated with an acceptable rate of toxicity, and patients with a MGMT promoter methylated status had a better survival. However, further prospective trials are needed to confirm these results.

P.104. SAFETY ANALYSIS OF RANDOMIZED BELGIAN PHASE II TRIAL OF EXTENDED USE OF ADJUVANT TEMOZOLOMIDE IN NEWLY DIAGNOSED GliOBlastOMA PATIENTS
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PURPOSE: We conduct a Belgian randomized phase II trial to determine whether prolonged administration of temozolomide (TMZ) in newly diagnosed GBM patients increases their progression-free survival (PFS). We also assess the safety profile of this extended use of TMZ since no data are available yet. METHODS: Patients with newly diagnosed glioblastoma presenting with a response or stable disease after the standard treatment of 6 months adjuvant TMZ, were included. These patients were randomized between continued treatment with TMZ or observation, using residual tumor and MGMT status as stratification factors. Patients randomized in the observation arm were rechallenged with TMZ upon progression. We will report here the PFS at 6 months and the safety analysis from the interim analysis. RESULTS: The first 20 patients included were comparable between both arms in terms of the well-known prognostic factors such as median age at diagnosis 55 vs 56 years, Karnofsky score 84 vs 92%, residual tumor in 8 vs 9 patients, and steroids use for 5 vs 2 patients in prolonged TMZ arm and observation arm, respectively. The progression-free survival (PFS) at 6 months was 70% vs 57%, respectively. The median number of cycles was 6 in the prolonged TMZ arm. Three patients presented with a complete response after 6 months of added TMZ. The mean number of all
grade toxicity per patient was 3.5 (+/− 3.3). The toxicities of TMZ were, in the majority of cases, limited to grade 1–2; 4 patients had an asymptomatic grade 3 lymphopenia, 3 had grade 3 asymptomatic thrombocytopenia, and 1 patient had grade 3 asymptomatic anemia. But only 1 patient out of the 10 included in this arm had to stop TMZ because of hematological toxicity. In the observation arm, 5 patients were rechallenged and 3 cycles were given without any response. Patients presented with grade 1 toxicity and only 1 patient had a grade 2 toxicity. Patients were able to finish therapy. CONCLUSION: Hematotoxicities are very infrequent in the prolonged adjuvant TMZ arm but only 1 patient had to stop treatment. This analysis shows a potential benefit of the experimental arm in terms of PFS at 6 months. Accrual is nearly completed and updated results on safety will be reported.

P.105. VAULTS AND THE MAJOR VAULT PROTEIN (MVP): IMPACT ON THE MALIGNANT PHENOTYPE OF HUMAN GLIOBLASTOMA MULTIFORME

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Vaults are highly conserved ribonucleoprotein particles containing a small untranslated RNA (vRNA). The 110-kDa major vault protein (MVP) has been implicated in the regulation of multiple cellular processes, including transcriptional mechanisms, chemoresistance, and several signaling cascades/molecules (eg, MAPK and PI3K pathway). While in normal brain the expression of MVP is very low, MVP expression is consistently upregulated in gliomas including glioblastoma multiforme (GBM). Aim of this study was to investigate whether MVP/vaults have an impact on GBM cell growth and aggressiveness, including chemotherapy responsiveness and to clarify underlying molecular mechanisms. MVP and MVP–GFP fusion proteins were overexpressed by plasmids and adenoviral constructs. Endogenous MVP expression was repressed by shRNA. Protein expressions were detected by immunofluorescence and Western blot. Consequences of MVP modulation on cell proliferation, migration, and invasion capacities were analyzed by growth curves, scratch and transwell-chamber assay, respectively. Moreover, tumor formation in dependence of MVP expression was tested in SCID mice. Ectopic MVP expression in MVP-negative H7 glioma cells led to a significantly enhanced proliferative and migratory potential in vitro. Especially responsiveness to epidermal growth factor (EGF)-mediated growth stimulation was increased parallelly by significant upregulation of MAPK and PI3K pathway indicated by phosphorylation of ERK and AKT, respectively. Accordingly, several signal mediators of these pathways, including PTEN and p66, were detected in immunoprecipitates from MVP-overexpressing cell clones. MVP transgenic cells were significantly resistant to cell death induced by serum-starvation but only marginally protected against the cytotoxic effects of diverse chemotherapeutics. Expression of a truncated MVP molecule harboring only the MVP-coiled domain and/or MVP down-modulation by shRNA in MVP-positive GBM cells induced programmed cell death as well as hyporesponsiveness to pro-death factor starvation. Tumor growth in SCID mice was significantly enhanced in all MVP overexpressing H7 subclones when compared with vector controls. Our data prove a significant contribution of vaults/MVP to the malignant phenotype of human GBM cells supporting activation of oncogenic signaling pathways and growth/survival factor responsiveness.

P.106. A FIVE-YEAR FOLLOW-UP EXPERIENCE IN NEWLY DIAGNOSED GLIOBLASTOMA AND CONCOMITANT PROTOCOL: TOLERANCE, COMPLIANCE, EFFECTIVENESS, AND SECOND-LINE THERAPIES

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Since 2005 the Stupp protocol with concomitant regimen of chemoradiotherapy followed by monthly adjuvant cycles of temozolomide has become the standard first-line approach in newly diagnosed glioblastoma after surgery. In this study, we present a 5-year follow-up experience in newly diagnosed glioblastoma treated with the concomitant protocol at the Neurosurgery Units of Policlinico and Galeazzi Institutes. From January 2005 to December 2009, we enrolled 91 patients eligible to complete the concomitant phase. We excluded patients in poor general or neurological conditions who needed a rehabilitation period prior to be submitted to radiotherapy. People over 70 years old were addressed to a modified protocol with a reduced dosage of radiotherapy, except for 3 patients in very excellent conditions who were submitted to standard protocol. There were 38 women and 53 men ranging from 18 to 75 years. All of them were submitted to gross total removal of the lesion (as assessed by postoperative gadolinium-enhanced CT or MRI scan) except for 6 deep-seated lesions, submitted to stereotactic biopsy. In 63 cases, MGMT status was analyzed. All the cases included in the concomitant phase of the protocol. In 4 cases, a reduced dose of temozolomide was administered because of the onset of paresthesia. In the adjuvant phase, we preferred to administer 12 monthly cycles of temozolomide instead of the standard 6 months regimen. In the majority of patients (90%), we adopted a modified schedule (150 mg/m2/day 1–5, 75 mg/m2/day 6–10 day). Four patients experienced a bronchopneumonia, 2 during the concomitant phase, and 2 during the adjuvant phase. At 6 months 100% of patients were alive, at 12 months 75% of patients, at 24 months 22%, and at 36 months 10%. Median survival was 15 months and median time tumor progression was 12 months. Twelve patients had second surgery at recurrence (in 9 of them Gliadel wafers were placed in the cavity), and 80% of the patients with recurrence received a second-line therapy: rechallenge of temozolomide (the 1-week on–one week off regimen in unmethylated tumors), fotemustine, bevacizumab. We also analyzed the quality of life of the patients, the clinical (Karnofsky score) and neuropsychological status (MMSE), the duration of hospital stay, and days spent in outpatients’ visits. Finally, we concluded that a good tolerance of the concomitant regimen was observed in the majority of patients, determining an acceptable quality of life and, thus, an improved access to second-line therapies.

P.107. UPDATED RESULTS OF A PHASE II TRIAL OF BEVACIZUMAB AND IRINOTECAN IN RELAPSED HIGH-GRADE GLIOMA

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BACKGROUND: Relapsed glioblastoma multiforme (GBM) has a poor response to current chemotherapy and prognosis of patients with recurrent disease is dismal, with a median survival of 3–6 months. Numeral trials using bevacizumab, a humanized IgG1 monoclonal antibody to vascular endothelial growth factor (VEGF), with or without chemotherapy, have reported excellent response rates using 10 mg/kg or 15 mg/kg every 2 weeks, and allowed expedite FDA approval for its use as a second-line treatment in relapsed GBM. We performed a phase II trial of bevacizumab using 5 mg/kg only, with irinotecan (CPT11) every 2 weeks as reported in the initial presentation by Stark Vance. In our interim analysis, we had demonstrated excellent response rates and similar results to others. This is an update of the final results. PATIENTS AND METHODS: This phase II trial accrued 30 patients with recurrent GBM who received bevacizumab at 5 mg/kg and CPT11 at 125 mg/m2 every 2 weeks, after failing radiation therapy and adjuvant TMZ. All patients on antiepileptic drugs (AEDs) had their regimen changed to nonenzyme-inducing AEDs (NEIAEDs) prior to receiving CPT11. Patients with KPS ≥ 50% were allowed regardless of prior relapses. Patients were evaluated clinically and with contrast-enhanced MRI scan every 4 treatments of bevacizumab until progression. RESULTS: All 30 patients were evaluable. Responses were assessed radiographically according to the MacDonald criteria and comparing T2 or Flair weighted Sequences: 19 patients (63%) had a documented response (CR + PR), 6 patients (20%) had stable disease (SD) and 5 patients (19%) progressed (PD). The average number of bevacizumab treatments received was 5.6 (1–20). The 6-month progression-free survival was 33.4%; 6-month overall survival was 66.7%; median overall survival was 8.7 months (36.3 weeks); median progression-free survival was 5 months (22.8 weeks). Several complications were reported: 3 DVTs and 2 PEs requiring IVC filter placement, 2 intracranial hemorrhages and 1 vascular complication. All patients were clinically and/or biochemically well. Patients were able to finish the concomitant phase of the protocol. In 4 cases, a reduced dose of temozolomide was administered because of the onset of paresthesia. In the adjuvant phase, we preferred to administer 12 monthly cycles of temozolomide instead of the standard 6 months regimen. In the majority of patients (90%), we adopted a modified schedule (150 mg/m2/day 1–5, 75 mg/m2/day 6–10 day). Four patients experienced a bronchopneumonia, 2 during the concomitant phase, and 2 during the adjuvant phase. At 6 months 100% of patients were alive, at 12 months 75% of patients, at 24 months 22%, and at 36 months 10%. Median survival was 15 months and median time tumor progression was 12 months. Twelve patients had second surgery at recurrence (in 9 of them Gliadel wafers were placed in the cavity), and 80% of the patients with recurrence received a second-line therapy: rechallenge of temozolomide (the 1-week on–one week off regimen in unmethylated tumors), fotemustine, bevacizumab. We also analyzed the quality of life of the patients, the clinical (Karnofsky score) and neuropsychological status (MMSE), the duration of hospital stay, and days spent in outpatients’ visits. Finally, we concluded that a good tolerance of the concomitant regimen was observed in the majority of patients, determining an acceptable quality of life and, thus, an improved access to second-line therapies.
P.109. EARLY INITIATION OF RADIOTHERAPY PLUS CONCOMITANT AND ADJUVANT TEMOZOLOMIDE (TMZ) AND OVERALL SURVIVAL (OS) IN GLIOBLASTOMA (GBM) PATIENTS

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OBJECTIVE: The influence of early start of radiotherapy plus concomitant and adjuvant temozolomide on overall survival (OS) in GBM patients was investigated. METHODS: Forty-eight consecutively histologically verified glioblastoma patients (median age 62.5 years, from 25 to 82, 19 females and 29 males, WHO performance status 0–1) received surgery (15 biopsy, 18 partial, and 14 complete resections) and radiotherapy (start median 17.5 days, from 12 to 27 days after surgery) with concomitant and adjuvant TMZ (all patients completed 60 Gy in 2 Gy/day fractions, 5 day/week, 40 of 46 completed concomitant TMZ, 18 of 40 additionally 6 cycles of adjuvant TMZ). No significant wound complications leading to revision surgery occurred. RESULTS: Altogether, the 12 of 24 month OS was 54/20.2% with a median survival of 13.7 months. In younger patient (<65 years, median 75.8, 28 patients), the 12 of 24 month OS was 68.4/34.3% with 16.9-month median survival, in older patient (>65 years, median 73, 20 patients) the 12 of 24 month OS was 28.8/5.8% with 7.7-month median survival (log-rank, P = 0.005). The OS comparing RT start <16 days with >16 days was not significantly different. Extent of surgery in patients OS in the young age group (biopsy vs complete: P = 0.06), but not in patients <65 years (P = 0.3). CONCLUSION: As the 12 of 24 month OS in our patients <65 years (median 77 years) is better than in the OS of the EORTC study (61.1/26.5%) with comparable demographics except for therapy start (EORTC median 3 weeks), we speculate that early start of the RT/TMZ might be of additional benefit.

P.110. PHASE II STUDY OF IFOSFAMIDE, CARBOPLATIN, AND ETOPOSIDE IN PATIENTS WITH A FIRST RECURRENTITY OF GLIOBLASTOMA MULTIFORME

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OBJECTIVE: The prognosis of recurrent glioblastoma multiforme (GBM) remains unsatisfactory. The authors conducted a Phase II study of ifosfamide, carboplatin, and etoposide (ICE) for a first recurrence of GBM to determine whether it prolonged a patient's good quality of life. METHODS: This trial was an open-label, single-center Phase II study. Forty-two patients with a first GBM relapse after surgery followed by standard radiotherapy (60 Gy) and first-line temozolomide- or nimustine-based chemotherapy were eligible to participate. The primary endpoint was progression-free survival (PFS) of 6 months after the ICE treatment (PFS-6), and secondary endpoints were response rate, toxicity, and overall survival. Chemotherapy consisted of ifosfamide (1000 mg/m2 on Days 1, 2, and 3), carboplatin (110 mg/m2 on Day 1), etoposide (120 mg/m2 on Days 1, 2, and 3), every 6 weeks. RESULTS: Progression-free survival at 6 months after ICE treatment was 35% (95% CI 22–50%). The median duration of PFS was 17 weeks (95% CI 10–24 weeks). The response rate was 25% (95% CI 9–34%). Adverse events were generally manageable, including nausea, vomiting, and neuropathy. CONCLUSIONS: This regimen was well tolerated and has some activity and could be one of the options for patients with recurrent GBM.

P.111. LONG-TERM SURVIVORS OF GLIOBLASTOMA

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There is no generally accepted definition of long-term GBM survivors (LTGBMs). Usually, most authors define long-term GBM survivor as a patient who survives at least 3 years after the histological diagnosis of glioblastoma. LTGBMs are uncommon and are reported to occur in 0.5%–16% of cases. In our ENOK (Ege University Neuro-Oncology Council) cases we have 12 of 572 GBM patients who survived more than 3 years (3.2%). The clinical and molecular factors that contribute to long-term survival are still unknown. Authors underline the association of glioblastoma long-term survival with prognostically favorable clinical factors, in particular young age and good initial performance score (KPS) as well as MGMT promoter hypermethylation.

P.112. HIGH-RESOLUTION GENOMIC PROFILING OF XENOGRAFTED HUMAN GLIOMAS TO DELINEATE NONANGIOGENIC AND HIGHLY ANGIOGENIC PHENOTYPES IN A CLINICALLY RELEVANT MODEL SYSTEM

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Glioblastoma multiforme (GBM) is the most common form of malignant brain cancer in adults. Patients with GBM have a uniformly poor prognosis, with a median survival of 1 year thus, advances on all scientific and clinical fronts are needed. We have developed a human glioblastoma xenograft model in nude rodents that is characterized by a highly infiltrative nonangiogenic phenotype. Upon serial transplantation, this phenotype will develop into a highly angiogenic tumor. Thus, we have developed an animal model where we are able to establish two characteristic tumor phenotypes that define human glioblastoma (ie, diffuse infiltration and high neovascularization). It is well established that the cancer genome is molded by the dual processes of somatic mutation and selection. In order to assess whether the observed phenotypic shift is because of clonal selection in vivo, we have performed high-resolution aCGH on primary tumors and xenografts derived thereof. We show that although the overall genomic pattern is highly conserved, additional genomic events trigger the switch from an invasive to a highly angiogenic phenotype observed in vivo. We are currently further analyzing our findings by applying whole exome sequencing to the analyzed samples to delineate the mutational evolution of xenografted gliomas at single-nucleotide resolution and identify new mutational events linked to the phenotypic switch. This molecular dissection of the 2 hallmarks of GBM could lead to the identification of potential biomarkers and facilitate the elucidation of the molecular pathways involved in the switch from invasive to angiogenic growth, thereby potentially opening new diagnostic and treatment avenues in the clinic.
P.114. IDENTIFICATION OF CD133+/TELOMERASELOW PROGENITOR CELLS IN GliOBLASTOMA-DERIVED CANCER STEM STELL LINES
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Glioblastoma multiforme (GBM) is paradigmatic for the investigation of cancer stem cells (CSC) in solid tumors. The CSC hypothesis implies that tumors are maintained by a rare subpopulation of CSC that gives rise to rapidly proliferating progenitor cells. Although the presence of progenitor cells is crucial for the CSC hypothesis, progenitor cells derived from GBM CSC are yet uncharacterized. Our data suggest that in the subgroup of CD133+ primary astrocytic GBM, CD133+/telomerase+ CSC give rise to non-tumorigenic, CD133+/telomerase− progenitor cells. The progenitor cell population proliferates rapidly resulting in significant telomere shortening when compared with the CD133+ compartment comprising CSC. The average difference in telomere length as determined by a modified multi-color flow FISH (fluorescence in situ hybridization) was 360 bp corresponding to 4–8 cell divisions. Taken together, we demonstrate that CD133+ primary astrocytic GBM comprise a rapidly proliferating, CD133+/telomerase− progenitor cell population in addition to CSC and terminally differentiated cells.

P.115. BEVACIZUMAB FOR THE TREATMENT OF PATIENTS WITH RECURRENT HIGH-Grade GLIOMA, RESULTS FROM A DUAL-CENTER CLINICAL EXPERIENCE IN BELGIUM
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BACKGROUND: Vascular endothelial growth factor (VEGF) plays a key role in the neo-angiogenesis that characterizes high-grade gliomas (HGG). Bevacizumab (BEV), a humanized immunoglobulin G1 monoclonal antibody that inhibits VEGF, has demonstrated activity against recurrent HGG. PATIENTS AND METHODS: Patients with progressive HGG following prior standard care (including at least surgery, radiotherapy, and temozolomide) who received BEV (at a dose of 10 mg/kg every 2 weeks or 15 mg/kg every 3 weeks) outside a clinical trial protocol were identified in 2 Belgian university hospitals. Tumor response and anti-edema effect were assessed by magnetic resonance imaging (MRI, including T1, T2, T1 contrast) at baseline, after the induction phase and thereafter. RESULTS: Twenty patients with recurrent HGG were identified (11 M, 9 F; median age 40 [range 28–70]); initial WHO grade: grade 2: 2 patients, grade 3: 4 patients, grade 4: 14 patients; baseline KPS: 90–80%: 3 patients, 70–60%: 17 patients. A median number of 3 prior systemic therapies had been administered. A total of 93 BEV administrations were performed (median 6, range 1–11). BEV-related toxicity consisted of CTCAE-grade 3 abdominal pain syndrome (1 patient), grade 3 skin ulceration (1 patient), grade 1 epistaxis (1 patient), grade 1 subungual bleeding (1 patient), and grade 1 hypertension (1 patient). There were no dose reductions. Fourteen patients stopped BEV because of tumor progression, 2 because of toxicity in the absence of a clinical response. At the time of this analysis, tumor response assessment by MRI is available for 14 patients; Response by T1 + Gd: 1 CR, 4 PR (BORR 36%); 11 of 14 patients (79%) had regression of edema on T2 FLAIR. A reduced uptake of amino-acid tracer on PET scan was documented in 3 of 4 patients at the time of MRI response. After a median follow-up of 8.5 months, 4 patients currently remain under treatment. Three out of 15 patients with sufficient follow-up remained progression-free after 6 months of BEV (with regression of all tumor related symptoms and the ability to maintain their personal and professional lives). CONCLUSIONS: In this analysis of the off-study use of BEV for recurrent HGG, activity and tolerability were comparable with what has been reported from prospective phase II trials. A meaningful subgroup of patients in this series derived a durable treatment effect with evidence for a metabolic response in addition to an edema reducing effect.

P.116. FUNCTIONAL VALIDATION OF NOVEL MOLECULAR TARGETS FOR ANTI-ANGIOGENIC TREATMENT OF MALIGNANT GLIOMAS
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Glioblastoma multiforme (GBM) remains one of the most malignant tumors in mankind. Despite a multimodal treatment, prognosis and survival of patients remain poor. The highly angiogenic properties of GBM make anti-angiogenic therapy an attractive addition to the current treatment protocol. Our group is currently active in identifying and characterizing novel biomarkers and therapeutic targets involved in the angiogenic switch observed in malignant gliomas. Making use of a clinically highly relevant xenograft model that recapitulates the invasive and angiogenic properties of GBM within consecutive generations of rats, we have previously performed a large-scale iTRAQ-based proteomics study comparing non-angiogenic to angiogenic GBM phenotypes. From more than a thousand quantifiable proteins identified in membrane fractions, about 50 proteins showed increased expression in angiogenic tumors, which may represent novel molecular targets for the development of anti-angiogenic therapy in the management of GBM.

P.117. BEVACIZUMAB AND FOTEMUSTINE AS SALVAGE THERAPY IN RECURRENT GLIOBLASTOMA: A PHASE II MULTICENTER ITALIAN STUDY
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BACKGROUND: Recent evidence indicates that antiangiogenic therapies have an important role in recurrent high-grade gliomas. Bevacizumab, a humanized monoclonal antibody against vascular endothelial growth factor (VEGF), has been reported to be active with acceptable toxicity. We report the preliminary results of a multicenter, open-label, non-randomized phase II study on bevacizumab plus fotemustine in GBMs recurrent after standard treatment (surgery, radiotherapy, and temozolomide) who received BEV (at a dose of 10 mg/kg every 2 weeks or 15 mg/kg every 3 weeks) outside a clinical trial protocol. Our group is currently active in identifying and characterizing novel biomarkers and therapeutic targets involved in the angiogenic switch observed in malignant gliomas. Making use of a clinically highly relevant xenograft model that recapitulates the invasive and angiogenic properties of GBM within consecutive generations of rats, we have previously performed a large-scale iTRAQ-based proteomics study comparing non-angiogenic to angiogenic GBM phenotypes. From more than a thousand quantifiable proteins identified in membrane fractions, about 50 proteins showed increased expression in angiogenic tumors, which may represent novel molecular targets for the development of anti-angiogenic therapy in the management of GBM.

Abstracts
patients. Forty percent of responders had unmethylated MGMT promoter. The most frequent side effects were: hematological grade 3–4 toxicity (21%); fatigue (46%); mild arterial hypertension (9%); and one grade III hypertension with reversible hypertensive encephalopathy; hemorrhagic events (12.5%) (2 lobar hematomas, 2 asymptomatic intratumoral bleedings, 1 subependymal bleeding); thrombotic events (9%) (one pulmonary embolism, 2 TVP, and 1 stroke); mild proteinuria (14%). CONCLUSIONS: Bevacizumab in combination with fotemustine was well tolerated and active in recurrent glioblastoma. The correlations between MGMT status, MRI perfusion, and response is ongoing.

P.118. RADIOTHERAPY AND CONCOMITANT AND ADJUVANT TEMOZOLOMIDE: TRANSLATION OF RANDOMIZED CONTROLLED CLINICAL TRIAL EVIDENCE INTO ROUTINE CLINICAL PRACTICE

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INTRODUCTION: Glioblastoma multiforme is the commonest primary malignant brain tumor in adults, and is usually rapidly fatal. Until 2004, standard treatment in the UK comprised excision of maximal surgical resection followed by radiotherapy. The most important advance in recent years has been the addition of concomitant and adjuvant temozolomide, which has been shown to improve overall survival in this group of patients. In addition, data have demonstrated differing outcomes for patients treated with temozolomide depending on the mutation status of the promoter region of the gene for methyl guanine methyl transferase (MGMT) within tumor tissue. MGMT is a DNA repair enzyme that may repair sublethal damage because of alkylating agents. Methylation of the promoter region of the gene may decrease levels of the enzyme in tumor tissue, with a consequent increase in cytotoxicity. METHODS: Trial patients often represent a highly selected group. We undertook a retrospective review of all patients with glioblastoma multiforme treated with concomitant temozolomide at our center between June 2005, when temozolomide was licensed in the UK for this indication, and December 2007. CONCLUSION: We demonstrate close correlation between our outcomes at a minimum follow up of 2 years with those seen in the sentinel trial. In addition, patients were assessed for tumor methylation status and again we demonstrate close correlation with published data. This clinical audit confirms that the benefit of this regimen can be translated into routine clinical practice within the National Health Service.

P.119. TREATMENT WITH MULTIKINASE INHIBITOR SORAFENIB FOR RECURRENT CENTRAL NERVOUS SYSTEM TUMORS

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OBJECTIVES: Treatment for recurrent central nervous system (CNS) tumors is limited. The multikinase inhibitor sorafenib induces apoptosis and blocks cell proliferation in a variety of tumors and cell lines. The response rate and safety was evaluated in a pilot series. PATIENTS AND METHODS: Twenty patients (3 women and 17 men) with recurrent CNS tumors received sorafenib 200 mg twice daily. The median age was 48 years (range from 23 to 65 years). Seven patients presented with GBM, 6 with anaplastic astrocytomas, 2 with ependymomas, 3 had meningiomas, 1 haemangiopericytoma, and 1 hemagioblastoma. All patients had previously received more than two lines of systemic treatment. RESULTS: Two (of 7) patients with GBM had partial remission (PR), lasting for 3–5 months, stable disease (SD) was observed for 2–7 months in 4 cases. One patient showed clinical and radiological progress (PD) 5 weeks after treatment start. Regarding anaplastic astrocytomas, 4 (of 6) patients showed SD for a time period of 2–9 months. Partial response in 2 patients was lasting for 5 months. In ependymomas, 1 PR (9 months) and 1 SD (8 months) was observed. Patient with hemangiopericytoma has still an SD for more than 20 months. After 7 months of therapy, patient with hemagioblastoma showed a progressive disease. The best achieved response within meningiomas was SD (1/3) for 6 months. Median time to progression for all patients was 3.5 months. Dose reduction was necessary in all patients mostly because of hypertension that was controlled with angiotensin-converting enzyme inhibitors or with antihypertensive combination therapy. More than 10 patients had skin changes similar to hand-foot syndrome grade II–IV. One gastrointestinal bleeding was reported, but no origin of hemorrhage was found. Some patients reported episodes of diarrhea which in one case lead to treatment discontinuation. Deep venous thrombosis was not observed in our patient cohort. CONCLUSION: Multikinase inhibitor sorafenib showed responses in heavily pretreated patients with recurrent CNS tumors.

P.120. ACTIVATION OF P53 BY MDMA2 ANTAGONISTS DOWN-REGULATES SURVIVIN AND INDUCES CYCLE ARREST AND APOPTOSIS IN HUMAN GLOBLASTOMA MULTIFORME

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Glioblastoma multiforme (GBM) is the most common and aggressive primary brain tumor in adults. Despite concerted efforts to improve current therapies and develop novel clinical approaches, patient survival remains poor, owing to the chemoresistant properties of glioblastoma. In fact, Currents, nutlins, small-molecular antagonists of MDM2, have been developed to inhibit the p53–MDM2 interaction and activate p53 signaling in cancer cells. We investigated whether nutlin-3a might be effective in inducing apoptosis in GBM. Glioma cell lines and primary cultured glioblastoma cells with known TP53 status were treated with nutlin-3a, and inhibition of cell growth and apoptosis induction were evaluated. Upon treatment with MDM2 antagonists, p53-dependent G2-M cell cycle arrest and apoptosis were effectively induced in p53–wild-type glioma cell lines. Nutlin-3a induced down-regulation of Survivin mRNA and protein expression together with up-regulation of PUMA mRNA and p21 and PUMA protein induction. In wild-type TP53 primary cultured glioblastoma cells, nutlin-3a-induced suppression of Survivin, overexpression of PUMA and/or Noxa proteins and apoptosis. Primary cultured glioblastoma cells and glioblastoma cells with mutant p53 or functionally impaired p53 pathway as a result of a polymorphism R72P are resistant to nutlin-3a apoptosis induction. The results suggest that MDM2 inhibition induced p53-dependent cell cycle arrest and apoptosis in wild-type TP53 glioblastoma cells. This effect seems to be at least partially because of Survivin down-regulation.

P.121. THE POTENTIAL ROLE OF SURGICAL RESECTION IN THE TREATMENT OF RECURRENT MALIGNANT GLIOMAS

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The founded relevance of surgical removal in the combined therapeutic strategy of malignant gliomas and the opportunity offered in the last few years by new unconventional treatments or second-line chemotherapeutic schedules have deeply modified the indications to surgical treatment of progressive and recurrent malignant gliomas. In the last 2 years, we have operated 22 recurrent malignant gliomas (12 glioblastoma, 7 anaplastic oligodendroglioma, and 3 anaplastic astrocytoma). At the moment of the initial diagnosis, all the patients have been submitted to first-line surgical treatment, radiotherapy, and chemotherapy with temozolomide, and/or photodynamic therapy, and 5 out of 22 cases showed documented localized tumor progression or recurrence at least 6 months after the previous surgery, and were evaluated suitable for second-line treatments. In 16 cases, it was possible to realize an extended resection (as radical as possible, if subtotal), and in 8 cases, during the same procedure, intratumoral CT wafers were positioned into the resection cavity. The main early complications of second surgical treatment have been local, as CSF fistula and wound dehiscence (4 cases), and were observed during the immediate postoperative period. Only in one case of temporal GBM, the second surgical resection was followed by an early progressive neurological deterioration, and the patient died 3 months after. The patients, followed in our department, with the relevant contribution of our home assistance service, have been submitted to second and/or third line chemotherapy; in 4 cases a highly used streptostatic radiotherapy has been given. The present preliminary data tend to confirm the relevance of surgical treatment
and subsequent combined treatments for recurrent malignant gliomas, providing for a median extension of overall survival of at least 8.5 months (3–15 months in the present series), with a significant improvement of neurological status and prompt resolution of intracranial hypertension. The results in terms of clinical benefit, progression-free survival, and overall survival will be presented, trying to design a patients’ setting with more specific indication at second surgical removal.

P.122. MANAGEMENT OF GYLOBLASTOMA MULTIFORME RECURRENCES
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Glioblastoma multiforme (GBM) is the most frequent form of brain tumor and is the most malignant astroglial neoplasm. GBM comprises 15%–20% of all primary intracranial tumors and >60% of astrocytic neoplasms. The incidence is in the range of 3–4 new cases per 100,000 population per year. It typically afflicts adults between 45 and 75 years of age, with a peak at 61.3. More than 80% of patients are older than 50. Despite progress in diagnostic procedures and treatment, prognosis in patients with GM is unfavorable and the median survival time is limited. The crucial prognostic signs are the patient’s general medical condition and the condition of the patient. If not treated, the patient dies within several weeks after the diagnosis has been made. Surgery prolongs survival for 8–10 months. Subsequent radiotherapy extends lifetime for an additional 3 months. Chemotherapy originally did not play an overly significant role. Only the introduction of new alkylating chemotherapy Temodal for primary brain tumor brought a more significant change resulting in prolongation of both overall survival (OS) and performance-free survival (PFS). These problems with recurrent GM are evoked again. Our aims are to evaluate surgical indications, and also to achieve the planning of general treatment strategy. We would like to point our treatment strategy for recurrent GBM for 15 patients group. The clinical and MRI follow-up of patients after first surgery (also during oncotherapy) will be carried out. Change of MRI often precedes change of clinical status. We assess as relapse of the tumor a growing mass more than 20%–30% of the neoplasm’s volume (using MRI volumetric evaluation), or the origination of a new tumor. PET/CT is used in the case of doubts about the reliability of differentiating the tumor’s relapse in the MRI image from other expansive, postcontrast enhancement processes (necrosis). We recommend for surgery the following patients: (a) Karnofsky Scale (KS) ≥70% and performance status (PS) WHO ≥2; (b) only local relapse, without multicentricity; (c) possibility of cytoreduction minimum 70% of the size. Our purposes are (a) obtaining maximally receivable radical surgery; (b) avoiding postoperative morbidity; (c) securing a sufficient amount of tumor tissue for histological, immunohistochemical, and cytogenetic investigation. Selected patient’s group benefit from recurrent GBM surgery supplemented by adequate subsequent oncotherapy has a positive effect on performance-free status and overall survival. We endeavor to adjust our treatment strategy based on these above mentioned assignment of a suitable treatment process for each subgroup. Surgery indication is only limited without a following oncotherapy. Indication for surgery, repeated radiotherapy, and chemotherapy remains a challenging task. A close cooperation between each of these neuro-oncology team members is essential for the good results.

P.123. AVASTIN-CAMPTO (AC) IN HIGH GRADE GLIOMA: ARE STANDARD MCDONALD’S CRITERIA APPROPRIATE TO ASSESS EFFICACY?
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INTRODUCTION: Since the publication in 2007 of the AC trials results in recurrent glioma, this treatment has widely been used and enables some improved survival benefit. The MRI evaluation is a standard practice to follow the treated patient. We observed discrepancies between T1Gado enhanced (Gado enh), T2 sequences, and the neurological patient outcome. OBJECTIVE: To analyze the Gado enh and T2 sequences every 3 months compared each other and to the base line at the onset of the treatment and clinical outcome in recurrent high-grade or transformed glioma.

PATIENTS AND METHODS: Recurrent glioblastoma (GBM) previously treated by radiotherapy (RT) and continuous temozolomide (TMZ) then monthly TMZ, and recurrent grade II–III glioma previously treated by RT and chemotherapy (CT). Avastin 10 mg/kg and Irinotecan 125 mg/m² were administered every 2 weeks until progression. MRI, clinical examination, and corticotherapy changes were performed every 3 months. RESULTS: A total of 44 patients were included in the study, 54% grade IV, 18% grade III and 13% transformed grade II–III. Performance status was 0–1 in 54%, 2 in 36%, and 3–4 in 9%, median age 54 (24–78), Ki67 <15% in 64%. Initial treatment was RT-TMZ and monthly TMZ in 66%, RT and CT in 34%. The median number of cycles was 9 (1–43). The median time to progression was 4.6 months. On MRI analysis of Gado enh sequence, the best response was PR 22.5%, SD 53% whereas PD occurred in 22.5%; in T2 sequence, the best response was PR 12.5%, SD 72.5%, and PD 15%. The median survival was 18 months from diagnosis and 6 months from the onset of the treatment. The concordance evaluated by kappa coefficient between Gado enh and T2 sequences was low at 0.32 (0.06–0.57). At 6 cycles of AC, the neurological status correlated well with both Gado enh and T2 sequences. DISCUSSION AND CONCLUSION: Despite McDonald’s criteria remain the tool usually used in glioma tumor situation, antangiogenic drugs lead to extend MRI evaluation to T2, or FLAIR sequences, so as to not be mistaken by false favorable response observed in Gado enh sequence. Decreased T1 enhancement cannot be considered an accurate marker of tumor mass in AC treatment.

LOW-GRADE GLIOMAS

P.124*. PROX1 IS A PREDICTOR OF SURVIVAL FOR ASTROCYTIC GLIOMAS BUT NOT FOR OLIGODENDROGLIOMAS GRADE II
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The clinical course of grade II gliomas remains variable and their transformation into a more malignant phenotype is highly unpredictable. There have been attempts to identify biological markers that can facilitate prediction of prognosis in individual cases of low-grade astrocytomas, but so far without much success. PROX1 is a transcription factor that plays a critical role in the development of various organs and that has been ascribed both oncogenic and tumor suppressive functions in human cancers. In a recent study, we have shown that PROX1 may act as a diagnostic marker for high-grade astrocytic gliomas. The aim of this study was to address the prognostic value of PROX1 in a cohort of patients with grade II gliomas. A retrospective chart review of all adults with grade II gliomas operated between 1982 and 1999 at the Uppsala University Hospital, Sweden, was performed. Eligible paraphlin-embedded tumor blocks were collected and a total of 128 samples were evaluated by immunohistochemistry for their PROX1 expression. The number of immunoreactive cells was used as a variable in multivariate survival analysis, together with established prognostic factors for this patient group. Patients with tumors showing high PROX1 expression had poor outcome, both in the univariate analysis (P = 0.0151) and multivariate analysis (P = 0.0210), compared with those with low PROX1 expression. When analyzing the separate histological subgroups, PROX1 expression was associated with shorter survival in astrocytomas and oligoastrocytomas but not in oligodendrogliomas. We conclude that PROX1 is a novel predictor of survival for grade II astrocytic gliomas.

P.125. PLEOMORPHIC GRANULAR CELL ASTROCYTOMA IN THE PINEAL GLAND
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BACKGROUND: Pleomorphic granular cell astrocytoma in the pineal region is exceedingly rare, and its clinicopathological features are distinctive. CASE REPORT: A 67-year-old woman was admitted with a staggering gait. Magnetic resonance imaging revealed a mass lesion at the pineal gland accompanied by obstructive hydrocephalus. Following surgery, pathological examinations demonstrated a pleomorphic granular cell astrocytoma. The patient has been free from recurrence for 24 months after surgery without adjuvant therapy. PATHOLOGICAL FINDINGS: The specimen exhibited nuclear and cytoplasmic pleomorphism. The nuclei varied in size, shape, and coarseness. Variability was also observed in the eosinophilic granular bodies, Rosenthal fibers, and spindle-shaped tumor cells. GFAP, S-100, and vimentin were immunohistochemically positive. Reticulin work-in-tum between the tumour cells, and granular cells with balloonated

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cytoplasm showed positive staining for PAS. DISCUSSION: Pleomorphic granular cell astrocytoma is believed to be a form of astrocytoma originating from the pineal gland. Its clinicopathological features resemble those of pleomorphic xanthoastrocytoma. However, it can be differentiated from the latter by the absence of reticulin fibers, absence of basement membrane between adjacent cells, and presence of large numbers of mitochondria.

P.126. RADICAL SURGERY AFTER CHEMOTHERAPY FOR WHO GRADE II GLIOMAS: A STRATEGY PROTECTING NEUROCOGNITION AND QUALITY OF LIFE (ABOUT A SERIES OF 12 PATIENTS)
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OBJECTIVE: The aim of this study was to evaluate the impact on cognition and quality of life (QOL) as well as the results of a temozolomide (tmz)-based chemotherapy (CT) delivered before a radical surgery for WHO grade II glioma With Organization (WHO) grade II gliomas. PATIENTS AND METHODS: We selected patients treated by tmz and then by surgery for a WHO grade II glioma, from the database of two French centers (Montpellier and Nancy). Usual oncological data were collected. Patients benefited from this intervention, at the end of the sequence, of a cognitive and QOL assessment. Global efficiency, laterality, executive functions, attention, information processing speed, psychomotor functioning, working memory, verbal and visual memory, language, visuo-spatial ability were considered for the cognitive assessment. Used tests will be presented. For the QOL, EORTC QLQ C30 + BN 20 scales were chosen. Radiological responses were evaluated by tumor volumes before and after CT and surgery. The presence of a gadolinium enhancement was systematically analyzed. RESULTS: Twelve patients with a median age at diagnosis of 40.5 years (22–51) and at assessment of 48 years (26–55.5) were selected. The median follow-up was 64 months (31.5–120) and the median time between assessment and the last surgery was 20.5 months (3–70). Symptoms at diagnosis were partial seizures in 4 (33.5%) cases and were generalized seizures in 8 (66.5%). Tumor location was frontal in 6 cases (3 right and 3 left), fronto-temporal in 4 cases (1 right, 3 left), and left temporal in 2 cases. Tmt alone has been prescribed for 11 patients and tmz + fotemustine for 1 patient. Clinical and radiological evaluation after chemotherapy will be detailed. Seven patients had one functional surgery, 3 had two procedures, and 2 had three procedures. Pre and postoperative volume will be clarified. After the last surgical procedure, 10 (83.3%) patients had a WHO grade II oligodendroglioma (4 with some anaplastic foci), 1 patient has a grade II astrocytoma, and 1 patient has a grade II oligoastrocytoma. Molecular data (including 1p19q status) will be presented. Analysis of neuropsychological and QOL data is in progress. Definitive data will be discussed. Preliminary results are in favor of the conservation of a high quality of cognition and QOL. CONCLUSIONS: The sequence “chemotherapy and then functional surgery” seems to protect cognitive functions and QOL for patients with WHO Grade II glioma even with multiple surgical procedures. Definitive results will be presented during the meeting.

P.127. THE BRAIN TUMOR EXPERIENCE FROM THE RELATIVES’ PERSPECTIVE
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INTRODUCTION: This research examined the experience of relatives of people suffering from a low-grade tumor using interpretative phenomenological accounts. There is a plethora of information about cancer in general, the care experience, and on adjustment to difficult situations. There is also a wealth of information from the medical and oncology literature providing the factual context to the brain tumor experience. However, there has been limited work carried out on how the family experiences and adjusts to a brain tumor diagnosis. Initial explorations have tended to examine patients and carers, and different types of brain tumors, as if they were universal phenomena. However, patients with brain tumors and their carers comprise a diverse group with a wide range of supportive care needs, depending on time since diagnosis and degree of malignancy. Therefore, the purpose of this study was to explore the specific experience of relatives of individuals recently diagnosed with a low-grade brain tumor. METHOD: A qualitative approach, based on interpretative phenomenological analysis (IPA), was adopted. Semistructured interviews were conducted with a purposive sample of 3 participants who were the spouse/partner of someone recently diagnosed with a low-grade brain tumor. Each interview was recorded and transcribed verbatim, and analyzed in accordance with IPA. RESULTS: Four superordinate themes emerged from the data including discovery, communication, emotional reactions, and contextual factors. Participants discussed the importance of discovering the tumor, both in terms of getting a diagnosis, and learning about the tumor. Disclosure and nondisclosure to others about the tumor diagnosis were also significant in the illness experience. An important theme to emerge involved the patients describing what they thought they were experiencing, and how they coped with this difficulty. The final theme placed the brain tumor experience within a wider context, where factors such as the relationship with the patient, relationship with professionals, and the hospital environment were described as significant. CONCLUSIONS: This research detailed the early tumor trajectory and the salient processes involved in this journey. A framework was proposed to help conceptualize the findings of the study and could be used to aid patients, families, and health professionals to reflect on, and better understand, parts of the early illness experience.

P.128. COMPARATIVE ANALYSIS OF IDHI MUTATION, TP53 MUTATION, AND MGMT HYPERMETHYLATION IN ASTROCYTOMAS
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TP53: mutation, MGMT hypermethylation and, more recently, IDHI mutations have been identified as precocious genetic aberrations in gliomas, but their mutual relationships during glioma formation have not been clarified. We performed a comparative genetic analysis in a selected group of 18 patients affected by low-grade astrocytomas and in these same patients at tumor recurrence, irrespective of anaplastic progression. The aim of the study was to investigate the natural history of disease, excluding the interference of chemo-therapeutic agents. MATERIALS AND METHODS: We studied 18 patients affected by fibrillary astrocytoma (9), gemistocytic astrocytoma (3), protoplasmic astrocytoma (6). They did not undergo radiotherapy or chemotherapy after first surgery. After a median follow-up of 72 months, 15 of 18 patients recurred and the tumor showed a more malignant phenotype. Three patients underwent a third curricular intervention, all progressing to more malignant phenotypes. Specimens were investigated for MGMT hypermethylation using methylation-specific PCR after sodium bisulfite modification; LOH on chromosomes 1p, 9p, 10q, 13q, 17p, and 19q; IDHI and TP53 mutations by sequencing analysis after PCR amplifications. RESULTS: Primary low-grade astrocytomas showed IDHI mutation in 17 out of 18 cases, MGMT hypermethylation in 8 out of 18, and TP53 mutation in 8 out of 14. At recurrence, all MGMT hypermethylation and IDHI and TP53 mutations in primary tumors were confirmed. Furthermore, all losses of heterozygosity observed in the first sample were present also at recurrence. While IDHI1 mutations were already present in all primary tumors but one, the MGMT and TP53 status showed changes at recurrence: 3 primary MGMT unmethylated tumors becomes hypermethylated at recurrence and one of them, initially wild type for TP53, showed a TP53 mutation. A possible predisposing role of IDHI toward accumulation of genetic aberrations was not investigated because of the small number of IDHI wild-type patients at primary tumor. Finally, 5 patients out of 8 with MGMT hypermethylated and 8 of 10 with MGMT unmethylated at primary surgery acquired new losses of heterozygosity at recurrence. CONCLUSIONS: IDHI mutation, MGMT hypermethylation, and TP53 mutations are precocious events in astrocytomas. Our results confirm that IDHI mutation is the earliest genetic aberration in these tumors and that is widely represented in low-grade astrocytomas. Interestingly, only tumors with unmethylated MGMT changed their methylation status becoming methylated.
PEDIATRIC BRAIN TUMORS

P.129*. FEASIBILITY AND TOLERABILITY OF INTRAVENTRICULAR THERAPY WITH ALTERNATING ETOPOSIDE AND LIPOSOMAL CYTARABINE: EXPERIENCE IN 33 CHILDREN WITH MALIGNANT BRAIN TUMORS

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Intrathecal chemotherapy is a crucial element in the treatment of leptomeningeal disseminated brain tumors in children. We report on our experience with an intraventricular therapy with alternating etoposide and liposomal cytarabine concomitantly to conventional and/or antiangiogenic chemotherapy. Since May 1998, patients received intrathecal etoposide at a dose of 0.25–0.5 mg × 5 days every 2–6 weeks for a total of 306 courses (1–41 per patient) via an Ommaya reservoir. Intrathecal methotrexate and mafosfamide were additionally administered to 10 and 2 children, respectively. From October 2004 on, liposomal cytarabine was added and 33 patients aged 8 months to 25 years with various intensively pretreated disseminated brain tumors received liposomal cytarabine (25–50 mg) via an Ommaya reservoir or sporadically by lumbar puncture (210 doses, 1–20 per patient). Dexamethasone was used concomitantly for 3–5 days to prevent arachnoiditis. To allow dose-intense treatment and potentially evade resistance, most patients received alternating courses of liposomal cytarabine and etoposide. Toxicities following liposomal cytarabine were headache (n = 10), nausea/vomiting (n = 8), ataxia (n = 1), meningoencephalitis (n = 2), and visual disturbance (n = 3), which were connected to benign cerebral hypertension in 4 children that improved after one time of pressure release by lumbar/intraventricular CSF removal. Etoposide was generally well tolerated, although mild toxicities occurred (headache, n = 2; nausea/vomiting, n = 1). Since 3 patients received concurrent anti-cancer therapy, the efficacy of intrathecal therapy cannot be assessed independently. In conclusion, liposomal cytarabine alternating with etoposide appears to be feasible and well tolerated. Known side effects of liposomal cytarabine might occur less frequently. The time intervals of treatment may be extended and bridged with etoposide.

P.130. OPTIC NERVE LOCALIZATION OF INTRACRANIAL GERM CELL TUMORS

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Intracranial germ cells tumors are usually localized along the midline (pineal 2 suprasellar) in Caucasians. Para axial tumors are mostly reported in Asian patients. Optic pathway germ cell tumors have been exceptionally reported. We report 3 of such cases in Caucasian patients. A 23-year-old male presented with raised intracranial pressure, requiring ventriculoperitoneal shunting. The MRI showed a large midline mass causing bitemporal hemianopsia and hydrocephalus, suggesting a pineal or suprasellar tumor. The biopsy showed a pure germinoma, no dissemination was found on MRI and markers were negative. Strategy was according to GCT 96 SIOP protocol: chemotherapy (Etoposide ifosfamide and Carboplatin) followed by a 24-Gy radiation to the ventricular system and tumoral bed. Six years later, he relapsed in the bulbomedullar junction, out of the irradiation field. A 13-year-old boy presented headache, diabetes insipidus, a growth retardation, and a right temporal mass lesion. A 96 SIOP protocol: chemotherapy (Etoposide ifosfamide and Carboplatin) followed by 54 Gy radiation of hypothalamus and pineal region. He relapsed 6 years later, in the bulbomedullar junction, out of the irradiation field. A 13-year-old female presented a diplopia with raised intracranial pressure, requiring ventriculoperitoneal shunting. The MRI showed a swelling of the right optic nerve, extending to the chiasm. Biopsy showed a pure germinoma, no dissemination was found on MRI and markers were negative. Strategy was according to GCT 96 SIOP protocol: chemotherapy (Etoposide ifosfamide and Carboplatin) followed by a 24-Gy radiation to the ventricular system and tumoral bed. Six years later, he relapsed in the bulbomedullar junction, out of the irradiation field. A 13-year-old female presented a diplopia with raised intracranial pressure, requiring ventriculoperitoneal shunting. The MRI showed a swelling of the right optic nerve, extending to the chiasm. Biopsy showed a pure germinoma, no dissemination was found on MRI and markers were negative. Strategy was according to GCT 96 SIOP protocol: chemotherapy (Etoposide ifosfamide and Carboplatin) followed by a 24-Gy radiation to the ventricular system and tumoral bed. Six years later, he relapsed in the bulbomedullar junction, out of the irradiation field.

P.131. RESULTS OF TREATMENT RECURRENT HIGH-GRADE GLIOM (HGG) WITH COMBINATION OF BEVACIZUMAB AND IRINOTECAN

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Recurrent HGG in children has a dismal prognosis with minimal improvements in survival seen following currently available salvage therapy. This study was conducted to determine if the combination of a novel antiangiogenic therapy, bevacizumab, and a cytotoxic agent, irinotecan, is safe and effective for pediatric patients with recurrent HGG. From February 2008 till December 2009, 22 patients with progressive HGG were enrolled in this study (11 girls and 11 boys). Age 12.5 years (range, 5–17 years). Previously all patients received resection of the tumor followed by RT with parallel temozolomide and monochemotherapy of temozolomide. Relapse was documented by CT/MRI/PET. Median of follow-up was 26.8 months (range 2–17 months). In 19 patients (86.3%), the glioblastoma (G) was histologically verified, and in 3 patients (13.7%) anaplastic astrocytoma (AA) was verified. Karnovsky was 50–100 (with median 80). All patients received 6-week cycles of combined therapy: bevacizumab 5 mg/kg + Irinotecan + G in 17 patients (mean dose of 243 mg/m²/day), 1, 15, and 29 mg/m² on day 1, day 8, 22, 29, 29 days. Median of follow-up was 6 months (range 1–18 months). Median of number of cycles for 1 patient was 3.8 (range 1–10). Objective response (complete and partial) observed in 10 patients (45.5%). CR in 4 patients, PR in 6, 4 patients in 10 patients. In 3 patients, PR in 6 patients, also PD in 6 patients (27.3%). Six-month PFS in all patients with HGG was 0.46, 12-month PFS was 0.19, 18-month PFS was 0.10; 6-month OS was 0.60, 12-month OS was 0.24, 18-month OS was 0.24. For the analyzed moment, 9 patients are still alive (40.9%), 1 patient died with PD died (59.1%); 1 patient with CR died in remission in 1.5 month after finishing therapy from leukoencephalopathy. The 18-month PFS in patients with GB was 0.11 and OS was 0.28. Objective response observed in 15 patients (78.9%); PD in 4 patients (21.1%). Median of OS was 10 months, median of PFS was 5 months. In all, 3 patients (100%) with AA was PD. Median of OS was 10 months and median of PFS was 7 months. No central nervous system hemorrhages occurred, but 1 patient developed leukoencephalopathy. Combination of bevacizumab and irinotecan is an effective in relapsed pediatric GB with acceptable toxicity. PFS in this group is higher than in patients with AA, what statistically proved (P = .05).

P.132. OVERVIEW OF CHILDREN WITH ANAPLASTIC ASTROCYTOMA

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INTRODUCTION. Anaplastic astrocytoma (AA) is a rare tumor of CNS in children, which differs from the adult prognosis if only surgical treatment performed. MATERIALS AND METHODS: From 2000 to 2005 37 pts at the age from 5 months to 16 years (median 8 years) with the first time verified AA were observed. 4 patients received only resection, 8 pts - resection and radiotherapy (RT), 25 pts - complex treatment (combination of resection, RT and chemotherapy (CHT)). Total resection of a tumor performed in 15 pts, subtotal - in 7 pts, partial - in 12 pts, biopsy - in 3 pts. 33 pts received RT in a dose of 50–60 Gy (median 55 Gy). CHT was carried out under various schemes depending on age. The pts under 3 years old (n = 6) received CHT by the protocol “Baby” POG. Pts older than 3 years received after RT: Temodal 200 mg/m² (n = 11), protocol HIT-91 (n = 5) or PCV (n = 3). RESULTS. The median of follow up was 46 months (7–150 months). 5-years PFS and OS for all group of pts was 40 ± 3% and 50 ± 9
% respectively. Medians of PFS and OS -24 and 60 mths respectively. PFS in pts with total resection was 69%, subtotal -42%, partial -10%, biopsy -0% (p = 0.01). 5-year PFS was 56% in pts with complex treatment, 10% - in pts with surgical treatment and RT or surgery alone (p = 0.02). In pts under 5 years 5-year PFS - 80%, older -24% (p = 0.002). The PFS in pts older 5 years who received different schemes of CHT was NS (not significant). CONCLUSIONS: The best indicators of CHT associated with complex resection of a tumor, age of pts older 5 years. The results permit to consider CHT as an effective and obligatory element of complex treatment of AA. The scheme of CHT choice depends on age of the patient.

P.135. A PREDICTIVE GENETIC MARKER FOR TUMOR RECURRENCE IN MENINGIOMAS

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INTRODUCTION: Meningiomas are tumors that arise from the coverings of the brain or the spinal cord. They are mostly benign and can often be surgically cured. However, in about 8% of the cases, an increased risk of tumor recurrence and a more aggressive clinical behavior are observed. Cytogenetically, meningiomas are well characterized with either a normal karyotype or monosomy of chromosome 22 in most of the tumors. Clinically relevant are also most common losses of the autosomes 1p, 9p, 14, and 18. The order of accumulating genetic aberrations has previously been estimated with oncogenetic tree models, and a genetic progression score (GPS) derived from these models was shown to be more predictive for tumor recurrence than WHO classification. MATERIALS AND METHODS: Fifty meningioma patients were operated by open surgery between 2008 and 2010. Tissue specimens from tumors were obtained after surgery and prepared for FISH analysis. According to our previous results, we used two-color FISH for chromosomal alterations of chromosomes 1, 9, 14, 18, and 22. RESULTS: In our cohort, 52% (26 of 50) correspond to WHO I, 40% (20 of 50) to WHO III meningiomas. The average age of all patients was 59.6 years ±11.4, 58.3 years (±11.4) of the female patients (32 of 50) and 63.4 years (±15.1) of the male patients (18 of 50). FISH analyses were performed in these 50 cases and for each meningioma up to 200 nuclei were evaluated. In 32 tumors, we found deletions of chromosome 22. In 22 cases, the deletion of the short arm of chromosome 1 was detectable. Loss of chromosome 14 was found in 13 cases, of chromosome 18 in 6 cases, and of 9p in 4 cases. On basis of these results, 27 cases correspond to a GPS of ≥1, 6 cases to a GPS of 1 ≤1 and <6.02 and 17 cases ≥6.02, indicating a higher risk of tumor recurrence. CONCLUSION: Grading and prognostic assessment of meningiomas can be controversial. The biological behavior of meningiomas can obviously not be reflected in histological parameters alone. Cytogenetic characterization of meningiomas by FISH analysis or by karyotyping can provide an insight into their potential of recurrence by GPS classification alone, and therefore a valuable criterion for the neurosurgeon's postoperative management protocol.

P.134. CRANIAL BASE MENINGIOMAS: THE ESSENTIAL ROLE OF STEREOTACTIC RADIOSURGERY

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INTRODUCTION: Surgical resection of cranial base meningiomas continues to present an enormous surgical challenge because of the complexity of the approaches and mainly of the possibility of disabling sequelae. In the past 2 decades, stereotactic radiosurgery has been advocated as the definitive treatment in the management of these tumors, as a first-line treatment or after incomplete resections, changing the current management protocols in the treatment of these meningiomas. MATERIALS AND METHODS: A retrospective review of 615 patients treated for single cranial base meningioma at our Gamma Knife Unit during the period 1993–2009 was performed, particularly selecting 233 cases followed for more than 2 years. RESULTS: Two-thirds of the patients were females, with a global median age of 55 (25–84). The most frequent location was the cavernous sinus (37%), followed by clival and petroclival regions (16.3%). Forty-five patients of these cases were followed on, and 65 patients had received previous radiotherapy. The mean treated volume was 11 cm3 (0.6–85). The mean follow-up time was 50 months (24–163), with 60 and 7 patients followed during more than 5 and 10 years, respectively. Volumetric control was obtained in 97% of patients, with a reduced volume in 71.2%, and stabilization in 26%. Clinically, 91% of patients remained stable, with an improvement in 2.5%. CONCLUSIONS: Gamma-knife radiosurgery is a safe and efficient technique in the control of cranial base meningiomas, with an excellent preservation of neurological function. It has displaced conventional radiotherapeutic treatments and is becoming a definite alternative to aggressive and potentially disabling surgical resections.

P.136. SURGICAL TREATMENT OF CENTRAL NERVOUS SYSTEM HEMANGIOPERICYTOMAS

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INTRODUCTION: Hemangiopericytomas (HPC) are rare, highly vascularized tumors derived from pericapillary cells or Zimmerman’s pericytes, which tend to recur locally and metastasize extracranially. Treatment includes complete surgical resection followed by radiotherapy to optimize local recurrence control. We present our experience in the treatment of patients with HPC. MATERIALS AND METHODS: Retrospective analysis of clinical data from patients with HPC treated at the Department of Neurosurgery between June 1995 and February 2010 was reviewed to establish lesion location, associated symptoms, radiological features, preoperative embolization, intraoperative findings, postoperative complications, extent of resection, recurrences, and need for adjuvant radiotherapy. RESULTS: A total of 14 patients with HPC were subjected to surgery during this period, of which 9 were females (64%) and 5 males (36%). Mean age of patients in this series was 44 years (range 21–75), and mean follow-up duration was 50 months (range 7–147). Lesions were supratentorial in 7 patients (50%), infratentorial in 2 (14%), falco-tentorial in 2 (14%) skull base in 2 (14%), and dorsal spine 1 (8%). Headache was the most frequent symptom in 8 cases (57%) followed by neurological deficits in 7 (50%). Endovascular therapy was used in 5 patients (35%). Complete surgical resection was achieved in 11 patients (78%) and subtotal resection in 3 (22%). Eight patients received postoperative radiotherapy (57%). Recurrences were observed in 5 patients (35%), 4 at the primary site, and 1 at the cranio-axial axis. Four of these patients were reoperated, and subsequently
treated with radiotherapy (75%). Five patients (36%) presented profuse intraoperative bleeding, and at most recent follow-up 1 patient had died (mortality 7%). DISCUSSION: HPC accounts for <1% of primary CNS tumors and about 2.2% of all meningeal tumors. Clinical presentation varies according to tumor size and location. The main differential diagnosis remains meningoima. Radiologically, irregular margins and heterogeneous enhancement have been associated with aggressive behavior. Surgical resection is the treatment of choice followed by radiotherapy with doses over 50 Gy. Local recurrence incidence ranges from 26% to 80% depending on the extent of primary resection and administration of radiotherapy. Extranearal metastasis rates range from 14% to 30% and are found predominantly in the bone, lungs, and liver, making strict follow-up mandatory.

CONCLUSION: Even a single clone with more advanced genetic progression meningoima shows considerable intratumoral cytogenetic heterogeneity, particularly in lack of other therapeutic options.

P.139. TREATMENT OF RECURRENT MENINGIOMAS WITH IMATINIB MESYLATE: A SINGLE-INSTITUTION EXPERIENCE
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BACKGROUND: Some irrespectable and symptomatic meningoima recur after conventional radiation therapy or stereotactic radiosurgery and present a therapeutic challenge. Evidence-based data for medical therapy for patients with malignant or recurrent and irresectable meningoima can be deemed as insufficient. Because of the prevalent expression of PDGF receptors in meningoima, imatinib mesylate, a tyrosine kinase inhibitor of PDGFR-alpha, -beta, c-kit, abl, and arg (Glivec-targets), has gained interest as a treatment of choice in this patient group. METHODS: We selected 18 patients with recurrent meningoima, aged 30–74 years (median 53.5 years), treated at our institution from 1996 to 2008. Nine patients (4 males, 5 females, median age 54.0 years) with positive immunohistochemical staining of at least one of the "Glivec-targets" were initiated with a daily oral dose of 400 mg imatinib mesylate as first-, second-, or third-line systemic therapy. MRI was performed every 3 months or at clinical suspicion of progression. The median time from diagnosis to start of imatinib treatment was 36 months. Immunohistochemical staining was performed on formalin-fixed and paraffin-embedded tumor tissue with antibodies against PDGFR-alpha, -beta, c-kit, arg, and abl. RESULTS: Imatinib mesylate at a dose of 400 mg/day was well tolerated. Of 9 patients treated with imatinib, 7 had stable disease and 2 progressed at the first scan after 3 months. We did not observe any complete or partial responses, though prolonged disease stabilization with a progression-free survival rate of 66.6% at 6 months could be observed. Overall median progression-free survival in the imatinib-treated cohort was 16 months (range: 1–31 months). Interestingly, imatinib treatment had a favorable impact on overall survival of meningoima patients (log-rank test, \( P = 0.34 \)). CONCLUSION: Single-agent imatinib mesylate is a well-tolerated therapeutic option with a high rate of disease stabilizations in recurrent meningoima. Imatinib treatment seems to correlate with survival in our patients despite heavy pretreatment with other therapeutic agents. Although these data clearly need verification in a larger, randomized clinical trial, our observation favors the use of imatinib mesylate in recurrent meningoima, particularly in lack of other therapeutic options.
INTRODUCTION: Neurofibromas are characteristic tumors of Neurofibromatosis type 1 (NF1). They arise as discrete or more diffuse plexiform tumors, growing along cutaneous and subcutaneous nerves and spinal roots. Primary spinal neurofibromas are present in at least 50% of NF1 patients, and in most cases are asymptomatic. They are very different from sporadic or Neurofibromatosis type 2–associated schwannomas in their cell composition, location, and behavior. There are scarce case reports and two small series with limited information, about clinical presentation and management of NF1 patients with spinal cord compression from spinal neurofibromas. The aim of the study was to review our experience in the management of these tumors. MATERIALS AND METHODS: A retrospective review of clinical data has been performed in our series of 205 NF1 patients, followed up, and treated in a neurofibromatosis referral center based in a neurosurgical unit. Pre- and postoperative neurological status has been evaluated following McCormick’s classification in patients with myelopathy secondary to spinal root neurofibromas. Demographic, clinical, anatomical, and surgical features were collected.RESULTS: Six surgical procedures for treatment of symptomatic spinal cord compression from neurofibromas have been performed in our series. Two surgical procedures at distant levels in 2 patients have been evaluated as 4 separated events. The clinical presentation ranged from 29 to 51 years. Clinical presentation was quadriparesis in 3, paraparesis in 1, and monoparesis in 2 cases. The anatomical level was cervical in 4 and thoraco-lumbar in 2. Tumor was growing from either anterior or posterior roots. Large intraspinal tumors were radically resected in every case, sparing rootlets with small tumor nodules, through laminectomies or osteoplastic laminotomies. Five surgical events were followed by an improved performance, with full recovery in 2 from 4 patients. One patient, suffering from a long-standing severe quadriparesis, saw no improvement with total tumor resection and significant neurological deficit was observed at follow-up. CONCLUSIONS: Spinal cord compression secondary to spinal root neurofibromas is a known but infrequently reported complication in NF1. The risk of becoming symptomatic does not decrease with age. The cervical area is where more neurofibromas appeared, but caudal spinal cord was also affected. Resection of spinal root neurofibromas producing symptomatic spinal cord compression is followed by excellent functional results, except in patients with long-lasting severe neurological deficit. Although asymptomatic spinal neurofibromas should not be treated, surgery should be considered and planned as soon as symptoms appear for the best functional results.

INTRODUCTION: Cauda equina paraganglioma (CEP) is a rare tumor. The first case was described in 1970 and since then less than 200 cases have been reported. The origin of CEP is uncertain as the existence of para-ganglia cells in the central nervous system remains a point of debate. There is an increased incidence in females and a male predominance, and low back pain is the main symptom in more than 90% of patients, with sciatica in 72%. MRI is the study of choice and treatment consists of total excision if feasible. Definitive diagnosis can only be made after immunohistochemical investigation. CEP is classified as Grade 1 tumors. Despite a favorable prognosis, recurrence rate varies from 5% to 14%. Clinically, the progression of the disease seems to be more related to tumor size than to histotype (WHO). Owing to the risk of neurological deficits, the treatment of CEP is surgical, as MRI features are not specific enough to differentiate CEP from other aggressive tumors of the cauda equina. At the Fundación Jiménez Díaz Neurosurgery Service, 19 cases of CEP have been surgically treated. The aim of this study is to describe the clinical aspects and the surgical management of these cases. MATERIALS AND METHODS: A series of 19 patients operated on between 1990 and 2016 will be analyzed. Clinical, surgical, and paraclinical data will be collected, including clinical presentation, surgical strategies, and postoperative follow-up. RESULTS: One hundred and sixty-eight procedures were performed by the same neurosurgeon (JMdC) in a VHL referral center. There were 13 men and 6 women (63% and 37%, respectively), with a mean age of 40.6 years (range 27–65 years). Eighteen intramedullary tumors were found, 1 inframedullary, and 1 extramedullary. The cervical area was affected in 2 cases, and the thoracic area in 17 cases. Large intraspinal tumors were radically resected in every case, sparing rootlets with small tumor nodules, through laminectomies or osteoplastic laminotomies. Two surgical procedures were performed at different levels in 2 patients. Two cases of recurrences were documented. In 1 patient, who underwent a new surgery, the tumor was not detected in a postoperative MRI. One patient died from tumor progression. CONCLUSIONS: CEP is a tumor with a low recurrence rate (5%–14%), with a clinical behavior suggestive of a benign tumor. In most cases, the diagnosis was made after surgery. The recurrence rate is low. Definitive diagnosis can only be made histologically. The patients treated at the Fundación Jiménez Díaz Neurosurgery Service show the microsurgical management results of spinal cord and brainstem paragangliomas in a VHL referral center.
P.145. BURKITT-LIKE LYMPHOMA REVEALED BY SPINAL CORD INVOLVEMENT
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Intradural spinal lymphoma accounts for only 3.3% of CNS lymphoma. It was mainly reported with immunodeficiency. Burkitt-like lymphoma (BL/L), also called atypical Burkitt lymphoma, is a rare high-grade lymphoma with characteristics on the borderline between large B-cell lymphoma (LBCL) and classical Burkitt lymphoma (BL). We report a case of primary intramedullary BL/L in an immunocompetent adult. CASE REPORT: A 62-year-old immunocompetent white man presented in November 2006 left leg weakness and unsteadiness. Immediate evolution was characterized by general polychemotherapy and intrathecal methotrexate. Treatment led to the diagnosis of Burkitt-like lymphoma. The patient was treated with liposomal cytarabine. He has been submitted to local radiotherapy RT and bone marrow infiltration. He has been offered ASCT from an HLA-matched sibling obtaining a complete remission 11 months after the involvement by myeloma. IgA1 MM was diagnosed at age 42 (November 2002) and submitted at VAD regimen with a partial response. In June 2003, he has been explored by ASCT from an HLA-matched sibling obtaining a complete remission that lasted until October 2005 when he recurred first at the sacral level, with neurological compression, increased paraprotein levels and bone marrow infiltration. He has been submitted to local radiotherapy RT and subsequently to thalidomide, and donor lymphocytes with persistence of the disease. Started on bortezomib attained the 2nd complete remission until September 2007 when new recurrence occurred. The patient was rechallenged with bortezomib with normalization of analytical parameters. After one more recurrence at the spine, he was diagnosed with leptomeningeal disease and started an intrathecal, systemic, and whole-brain radiotherapy therapy 30 Gy/10 # in May 2009. He obtained a complete response at CNS level and is alive and free of disease at 11 months after RT was done. CONCLUSIONS: Among the rare uncommon localizations of MM in the CNS, myelomatous meningitis may also occur. Different modalities of treatment are used, including intrathecal chemotherapy, cranial irradiation, and systemic chemotherapy. Patients with CNS myeloma even with aggressive treatment have extremely poor prognosis with <3 month disease-free survival. However, the patient is still alive at 11 months after the involvement of CNS by MM has been diagnosed.

P.144*. THE ROLE OF TEMOZOLOMIDE FOR PATIENTS WITH METASTATIC BRAIN DISEASE

BACKGROUND: Standards of chemo- and chemo-radiotherapy for treatment of brain metastases is not available till present time. Purpose of this trial is to assess the efficacy of temozolomide (TMZ) as monotherapy, TMZ combined with whole brain irradiation (WBI), or combined chemotherapy of TMZ and irinotecan (I) and TMZ and cisplatin (DDP) in patients with brain metastases (BM) from non-small cell lung cancer (NSCLC), breast cancer (BC), or melanoma. METHODS: Ninety-seven patients were reviewed. Patient characteristics were compared with different TMZ regimens. RESULTS: TMZ was incorporated in 150 mg/m2/day orally on days 1–5, every 4 weeks. Seven patients with melanoma were treated with combined chemotherapy of DDP (20 mg/m2/day intravenously on days 1–5, every 4 weeks) and TMZ (150 mg/m2/day orally on days 1–5, every 4 weeks). RESULTS: Observations of the
study were as follows: in the TMZ + WBI-treated patients with BM from NSCLC, 3 (14.3%) complete response (CR), 8 (38.1%) partial response (PR), 8 (38.1%) stabilization of disease (SD). The median overall survival (mOS) was 7.5 months. In the TMZ + WBI patients with BM from melanoma, 3 (17.6%) PR, 9 (52.9%) SD. The mOS was 6.6 months. Among patients with BC brain metastases, 1 (11.8%) CR, 11 (64.7%) PR, 3 (17.6%) SD. The mOS was 11 months. In the TMZ monotherapy patients with BM from NSCLC, there were 4 SD, 3 patients progressed. The mOS was 8 months. In the TMZ as monotherapy patients with BM from melanoma, 1 (5.9%) CR, 4 (23.5%) PR, and 7 (41.2%) SD. The mOS was 6 months. In the TMZ + IB patients with NSCLC brain metastases, 7 (63.6%) SD was 8 months. In the TMZ + DDP patients with melanoma brain metastases, 2 PR, 4 SD, 1 patient progressed. The mOS was 8 months. CONCLUSIONS: TMZ with WBI showed high efficacy in patients with BM from NSCLC, BC, and melanoma. TMZ as monotherapy showed efficacy and good tolerability in patients with BM from melanoma and SD in patients with BM from NSCLC. Combined chemotherapy of TMZ and I in heavily pretreated patients with NSCLC BM showed prolonged SD and good tolerability. The TMZ + DDP combination has pronounced high anticancer activity in patients with brain metastases from melanoma.

P.149* IRRADIATED TUMOR VOLUME INFLUENCES LOCAL CONTROL AND PROGRESSION-FREE SURVIVAL IN PATIENTS WITH 1–3 BRAIN METASTASES TREATED BY RADIOSURGERY H. L. van der Weide, S. L. de Kunder, R. M. A. Houben, G. Bosmans, P. Lambin, B. G. Baumert; Maastro Clinic, Maasstricht, Netherlands

OBJECTIVE: To evaluate the efficacy and clinical and radiological follow-up (r-FU) of patients with brain metastases (BM) treated with radiosurgery at a single institute. MATERIAL AND METHODS: Between 2003 and July 2008, 150 patients with BM (61.6% solitary, 61.9% lung) were treated with either (r-FU) of patients with brain metastases (BM) treated with radiosurgery at a single institute. The shorter PFS for patients treated by SRT also reflects this volume effect as compared to SRS. The maximum dose, corrected for fraction dose (EQD2, HR = 0.98/Gy; 95% CI 0.97–0.99). Toxicity (acute or late) grade ≥ 3 was observed in 13 patients, there was no significant difference between patients treated with SRS or SRT. Full 3D radiological evaluation of LC is ongoing and the results will be presented. CONCLUSIONS: There is a clear correlation between the total irradiated target volume on r-FU and local control: with increasing metastasis volume, a decrease of local control and r-FU is obtained. The shorter PFS for patients treated by SRT also reflects this volume effect as compared to SRS. The maximum dose, corrected for fraction dose (EQD2, α/β = 10) was a significant factor for LC (HR = 0.98/Gy; 95% CI 0.97–0.99). Toxicity (acute or late) grade ≥ 3 was observed in 13 patients, there was no significant difference between patients treated with SRS or SRT. Full 3D radiological evaluation of LC is ongoing and the results will be presented. CONCLUSIONS: There is a clear correlation between the total irradiated target volume on r-FU and local control: with increasing metastasis volume, a decrease of local control and r-FU is obtained. The shorter PFS for patients treated by SRT also reflects this volume effect as compared to SRS.

P.151* SUBACUTE NEUROLOGICAL SYNDROME WITH IMAGING CORRELATE FOLLOWING INTRATRACHEAL METHOTREXATE IN AN ADULT G. von Geldern, M. M. Mrugala, and B. Distad; University of Washington, Dept. of Neurology, Seattle, WA

BACKGROUND: Methotrexate (MTX) is an important chemotherapeutic agent in the management of oncolgical and autoimmune diseases. It can be given intravenously or intrathecally and is frequently given in combination with other drugs. Methotrexate has been implicated in a variety of neurological complications. The acute or subacute neurotoxicity occurs within days to weeks after MTX therapy and is characterized by acute onset of focal neurological symptoms and mimics cerebrovascular stroke. While this syndrome has been described in several case report series in children, it is much less frequently seen in adults. OBJECTIVES: To describe the clinical course of a patient with subacute toxicity after intratracheal MTX and the corresponding abnormalities on imaging.

METHODS: Case presentation and literature review. RESULTS: We report the case of a 29-year-old woman with acute systemic T-cell leukaemia receiving systemic low-dose MTX, cytarabine, cyclophosphamide, doxorubicin, vincristine, and Peg-Asparaginase, as well as intratracheal methotrexate. Eighteen days after intravenous chemotherapy and 8 days after her seventh intratracheal MTX application, she presented with acute onset severe aphasia and difficulty mild right face and arm weakness. Cerebrospinal fluid was unremarkable. Magnet resonance imaging (MRI) of the brain revealed confluent restricted diffusion in the left greater than the right centrum semiovale and focally within the splenium of the corpus callosum. These lesion had no significant mass effect, no associated neurological deterioration. Prognostic factors known from literature were evaluated and comparisons between SRS and SRT treatments were made. All imaging was fused to the baseline scan to obtain 3D information. All data were analyzed using univariate survival analyses. RESULTS: A total of 260 BM were irradiated, for 66% r-FU was available (23% had no r-FU because of early death). The median OS, PFS, and LC was 7.0 months (range 3 days–46 months), 4.0, and 6.0 months, respectively. There was a significant difference in OS between RPA classes (P < .001). Median PFS was 5.0 and 3.0 months for SRS and SRT treatment, respectively (P = .001). The 6 and 12 months, the LC rate was 46% and 37%. The sum of all target volumes irradiated per patient (PTV) was a significant prognostic factor for PFS (HR = 1.12/3 c in increase in PTV; 95% CI 1.01–1.23); PTV was a significant prognostic factor for LC (HR = 1.15; 95% CI 1.04–1.27). The maximum dose, corrected for fraction dose (EQD2, α/β = 10) was a significant factor for LC (HR = 0.98/Gy; 95% CI 0.97–0.99). Toxicity (acute or late) grade ≥ 3 was observed in 13 patients, there was no significant difference between patients treated with SRS or SRT. Full 3D radiological evaluation of LC is ongoing and the results will be presented. CONCLUSIONS: There is a clear correlation between the total irradiated target volume on r-FU and local control: with increasing metastasis volume, a decrease of local control and r-FU is obtained. The shorter PFS for patients treated by SRT also reflects this volume effect as compared to SRS. The maximum dose, corrected for fraction dose (EQD2, α/β = 10) was a significant factor for LC (HR = 0.98/Gy; 95% CI 0.97–0.99). Toxicity (acute or late) grade ≥ 3 was observed in 13 patients, there was no significant difference between patients treated with SRS or SRT. Full 3D radiological evaluation of LC is ongoing and the results will be presented. CONCLUSIONS: There is a clear correlation between the total irradiated target volume on r-FU and local control: with increasing metastasis volume, a decrease of local control and r-FU is obtained. The shorter PFS for patients treated by SRT also reflects this volume effect as compared to SRS.

P.150. MULTIDISCIPLINARY TREATMENT OF LEPTOMENINGEAL METASTASIS IN PATIENTS WITH LUNG ADENOCARCINOMA K. Mitsuya, T. Takahashi, H. Harada, S. Horiguchi, N. Yamamoto, Y. Nakasu, and T. Nishimura; Shizuoka Cancer Center, Nagaizumi, Japan

BACKGROUND: Leptomeningeal metastasis (LM) is a devastating complication of systemic cancer. New therapies that effectively treat primary cancers outside the CNS have underscored the significance of LM. Intrathecal chemotherapy plus radiation (RT) are less effective for LM in lung cancer. We retrospectively studied outcome of patients with LM from lung adenocarcinoma undergone multidisciplinary treatment in our institute. METHODS AND RESULTS: Between December 2004 and August 2009, 29 patients with LM from solid cancer underwent treatment. Eleven of 29 patients had lung adenocarcinoma; 7 of 11 presented with increased intracranial pressure, and other 3 with truncal ataxia. Treatment was indicated when LM was confirmed on MR images or cytology. Karnofsky performance score was more than 40, and life expectancy was more than 3 months if LM was controlled. The choice of treatment was based on clinical symptoms depending on the individual situation. Seven patients underwent intrathecal chemotherapy plus RT, EGFR-TKI plus RT, or VP-shunt plus RT (group A). Four patients underwent all of EGFR-TKI, RT, and VP-shunt (group B). Mean time to LM onset from diagnosis of lung adenocarcinoma was 24 (8–36) months. Mean survival time from LM onset was 4 months in group A and 9 months in group B (P = .029). Ten of 11 patients died; 9 of CNS metastases and 1 from pneumonia. No patients suffered from peritoneal carcinomatosis after VP-shunt. CONCLUSION: Combination of triple modalities (EGFR-TKI, RT, and VP-shunt) is a safe treatment, and may improve outcome of patients with LM from lung adenocarcinoma.

NEUROTOXICITY AND NEUROPROTECTION

P.152. VERIFICATION FOR HEMATOLOGICAL TOXICITY OF TEMOZOLOMIDE M. Okawa, T. Ito, K. Sato, Y. Ozaki, and H. Nakamura; Nakamura Memorial Hospital, Sapporo, Japan

INTRODUCTION: Although 4 years has passed after temozolomide started to be sold on the open market, there are a few reports regarding the hematological toxicity of temozolomide in Japan. We have examined for our own experiments in 62 cases. METHODS AND RESULTS: Sixty-two cases of initial and...
P.153. HLA-DQ2 + INDIVIDUALS ARE SUSCEPTIBLE TO HU-ANTIBODY ASSOCIATED PARANEOPLASTIC NEUROLOGICAL SYNDROMES

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BACKGROUND: Hu-antibody–associated paraneoplastic neurological syndromes (Hu-PNS) are diagnosed in patients with severe and subacute neurological syndromes through detection of high-titer Hu antibodies (Hu-Ab) in serum. Hu-Ab are directed against the neuronal HuD-antigen that is aberrantly expressed by all small-cell lung-cancers (SCLC). This ectopic expression hypothetically causes an autoimmune response, which has a positive antitumor effect, but also causes devastating neurological damage. The precise immunopathogenic mechanism of the neurological damage is unknown, although occurrence of both B- and T-cell–mediated immune responses in Hu-PNS indicates a role for cellular immunity. OBJECTIVE: We aimed to identify genetic risk factors for Hu-PNS and find any external test was used to compare the frequencies of the different HLA antigens in patients and controls. RESULTS: The frequency of HLA-DQ2 was significantly higher in Hu-PNS patients (33 of 53; 62%) than in HC (881 of 2395; 25%) (P < .0001), than those without well-defined antibodies (n = 11). Also more patients (P = .0192) without diagnosed malignancy (n = 34) survived when compared with cancer patients (n = 15). CONCLUSION: The presence of well-defined onconeuronal antibodies in Hu-PNS patients is associated with better prognosis. Among well-defined onconeuronal antibodies, anti-Yo are predisposing to 3-year survival in Western Poland population.

P.154. A FIVE-YEAR FOLLOW-UP OF NEUROLOGICAL PARANEOPLASTIC SYNDROME PATIENTS IN WESTERN POLAND POPULATION

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INTRODUCTION: Neurological paraneoplastic syndromes (PNSs) are considered as rare, immune-mediated remote effects of systemic malignancy on nervous system. Long-term observations are not commonly performed and until now—in Polish population. The aim of this study was to evaluate the survival of PNS patients and its association with diagnosed malignancy as well as with onconeuronal antibodies (ONAs). MATERIALS AND METHODS: The study included 177 PNS patients originating from Western Poland. In sera of all subjects, indirect fluorescence (EUROIMMUN, Germany) was performed as a screening and Western blotting (EUROIMMUN) as a confirmation test for the presence of ONA. The diagnosis of PNS was based on Graus' criteria. Five years after confirmation of onconeuronal antibodies, the follow-up was performed in 57 patients after obtaining informed consent. Data for follow-up originated from medical records, personal (out-patients clinic) or telephone contact. RESULTS: A 5-year follow-up was performed in 57 patients, and malignancy was found in 11 cases. In 8 patients, primary tumor was diagnosed before or at the time of onset of PNS symptoms. The most common was lung cancer (32%), breast cancer (16%), ovarian cancer (16%), Hodgkin lymphoma (10.5%), and prostate cancer (10.5%). In the studied group, 16 patients had anti-Hu antibodies, 14 had anti-Ri, 14 had anti-Yo, 7 were unidentified, and 6 were seronegative. During the follow-up period, 8 patients died, 4 with diagnosed neoplasm, 6 had well-defined onconeuronal antibodies (5 with anti-Hu and 3 with anti-Ri). The number of patients with well-defined onconeuronal antibodies who survived 5-year period was higher (n = 38; P < .0001), than those without well-defined antibodies (n = 11). Also more patients (P = .0192) without diagnosed malignancy (n = 34) survived when compared with cancer patients (n = 15). CONCLUSION: The presence of well-defined onconeuronal antibodies in PNS patients is associated with better prognosis. Among well-defined onconeuronal antibodies, anti-Yo are predisposing to 3-year survival in Western Poland population.
The patients were seizure-free in the pre-surgery phase (3 days up to 4 weeks before surgery), 88% in the 48-hour post-surgery phase and 84% in the early follow-up phase (48 hours to 4 weeks post surgery). Treatment failure after dose escalation to 3000 mg/day occurred in 3 patients. No serious adverse events related to the treatment with LEV occurred. CONCLUSIONS: Our data show the feasibility and safety of oral and intravenous LEV in the perioperative treatment of tumor-related seizures. Although this was a single-arm study, the efficacy of LEV appears to be promising. Considering the side effects and interactions of other anticonvulsants, LEV seems to be a favorable choice in the perioperative treatment of brain tumor-related seizures.

**Supportive and Palliative Care**

**P.156**: CLASSIFICATION OF HEADACHE IN PATIENTS WITH MALIGNANT GliOMAS ACCORDING TO THE INTERNATIONAL HEADACHE SOCIETY (IHS) CRITERIA

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BACKGROUND: Approximately 50% of patients with malignant primary brain tumors suffer from headache. However, well-designed clinical studies concerning this frequent and heterogeneous neurological symptom are rare. The aim of the study was to investigate the frequency and clinical features of headache in the course of disease of patients with malignant gliomas.

METHODS: We included 36 consecutive patients with supratentorial malignant gliomas in a prospective consecutive study. All patients were recruited from a Neuro-oncology outpatient unit. Using a standardized protocol, information concerning different aspects of brain tumor headache and general descriptive data were obtained. Patients were investigated at the time of diagnosis of the brain tumor, during concomitant radiochemotherapy, and at time of tumor progression.

RESULTS: At diagnosis, 47% of all patients reported headache. Among these, according to the IHS criteria, tension-type headache was as frequent as migraine-like headache (each 41%). Headache as the first symptom of the brain tumor was present in 39% of patients. During the concomitant treatment period, 56% of all patients reported headache. The proportion of tension-type headache increased to 70%, whereas migraine-like headache decreased to 15%. At the time of tumor progression, all patients reported tension-type headache.

CONCLUSIONS: Our results reveal that according to the clinical diagnostic criteria (IHS: 7.4.1), headache increased to 70%, whereas migraine-like headache decreased to 15%. At the time of tumor progression, all patients reported tension-type headache. The use of a diagnostic criteria for “headache attributed to increased intracranial pressure or hydrocephalus caused by neoplasm” (IHS 7.4.1) were not fulfilled at any time. At diagnosis, 76% of the patients met the IHS criteria 7.4.2 for “headache attributed directly to neoplasm.” Only 10% of patients fulfilled these IHS criteria at the time of concomitant treatment, and no patient during tumor progression.

**P.158**: INTRACTABLE HEADACHE BECAUSE OF NEOPLASTIC Meningitis IN two patients with Glioblastoma

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INTRODUCTION: Neoplastic meningitis in patients with malignant gliomas is rare complication in the advanced stage of the disease. Diagnosis of neoplastic meningitis can often be time consuming and misleading. From the clinical point of view, patients suffer from rapid neurological deterioration and intractable headache. In accordance with neurological signs and symptoms, the diagnosis can be established by MRI of the total neuraxis.

CASE STUDIES: One 37-year-old male and a 50-year-old female patient with glioblastoma received standard surgery and adjuvant radiochemotherapy. First patient developed headache 5 months after end of adjuvant treatment and second patient during concomitant treatment. Both patients experienced severe headache, not responding to steroids or conventional analgesics. High dosages of opiates showed only little clinical efficacy. The diagnosis of neoplastic meningitis was established by means of MRI of the neuraxis, showing typical enhancement of the meninges and contrast-enhancing bulky lesions together with neurological signs and symptoms. Because of rapid clinical decline, only supportive management was applied in both patients. Patients died shortly after the diagnosis of neoplastic meningitis.

CONCLUSIONS: This investigation reveals that according to the clinical diagnostic criteria (IHS: 7.4.1), “headache attributed to elevated intracranial pressure”, and also “headache attributed directly to neoplasm” (IHS: 7.4.2), can rarely be a diagnosed in patients with malignant gliomas. We recommend a modification of the diagnostic criteria of the IHS classification system for headache in patients with malignant gliomas.

**Primary central nervous system lymphoma (PCNSL)**

**P.157**: INTRAVENOUS AND ORAL LEVETIRACETAM IN patients with a SUSPECTED PRIMARY brain TUMOR AND SYMPTOMATIC EPILEPSY UNDERGOING NEUROSURGERY: THE HELLO STUDY

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BACKGROUND: Levitiracetam (LEV) is a newer anticonvulsant with a favorable safety profile. There are no relevant drug interactions, and an intravenous formulation is available. Therefore, LEV might be a suitable drug for the perioperative anticonvulsive therapy for patients with suspected brain tumors undergoing neurosurgery.

METHODS: In this prospective study (NCT00571155), patients with suspected primary brain tumors and tumor-related seizures were peroperatively treated with oral and intravenous LEV up to 4 weeks before and until 4 weeks after a planned neurosurgical procedure.

RESULTS: A total of 30 patients with brain tumor-related seizures and planned neurosurgery were included. Three patients did not undergo the planned surgery after enrollment, 2 patients were lost for follow-up. Therefore, 25 patients were fully evaluable. After initiation of therapy with LEV 100% of the patients were seizure-free in the pre-surgery phase (3 days up to 4 weeks before surgery), 88% in the 48-hour post-surgery phase and 84% in the early follow-up phase (48 hours to 4 weeks post surgery). Treatment failure after dose escalation to 3000 mg/day occurred in 3 patients. No serious adverse events related to the treatment with LEV occurred. CONCLUSIONS: Our data show the feasibility and safety of oral and intravenous LEV in the perioperative treatment of tumor-related seizures. Although this was a single-arm study, the efficacy of LEV appears to be promising. Considering the side effects and interactions of other anticonvulsants, LEV seems to be a favorable choice in the perioperative treatment of brain tumor-related seizures.
were tumor infiltration rather than chronic vascular disease may have prompted earlier diagnosis. LC has a variable presentation. A high index of suspicion is necessary to make the diagnosis. Early recognition is important since treatment can lead to prolonged survival or cure.

P.160*. PROGNOSTIC VALUE OF SERUM SOLUBLE INTERLEUKIN-2 RECEPTOR IN PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA
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Soluble interleukin-2 receptor (sIL-2R) is well known as a disease marker of systemic malignant lymphomas. However, clinical significance of sIL-2R in primary central nervous system lymphoma (PCNSL) is still unclear. We investigated relationships between serum sIL-2R or other clinical values and the prognosis in patients with PCNSL. The patients were 14 men and 12 women, mean age 66.9 years, treated in our hospital from November 2002 to August 2009. Mean follow-up period was 16.8 months ranging from 1 to 86 months. For the statistical analysis, the patients were grouped by the age (cut off: 70 years), the serum level of sIL-2R (cut off: 550 IU/mL) and LDH (cut off: 220 U/mL) before the treatment, and the treatment with or without methotrexate-based chemotherapy. The serum level of sIL-2R was not affected by the age. Kaplan–Meier analysis exhibited the tendency of poor survival among the aged population (P = .103). Higher serum level of sIL-2R related to the poor survival (P = .015), whereas no significant impacts of serum LDH level and chemotherapy were observed on the prognosis. Multivariate analysis using Cox proportional hazard model showed the serum level of sIL-2R was significantly associated with the prognosis (P = .025). Our study suggests that the measurement of serum sIL-2R might be useful as a prognostic indicator for PCNSL patients.

NEW DEVELOPMENTS IN SURGERY

P.161. EXTENT OF RESECTION AND OVERALL SURVIVAL AFTER INTRAOPERATIVE IMAGE-GUIDED BRAIN TUMOR SURGERY
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OBJECTIVE: The use of intraoperative MRI (iMRI) has been reported to improve the extent of resection in glioma surgery, indirectly influencing survival. Yet, randomized or at least comparative studies to prove its usefulness are lacking. With this analysis, we aim to assess the influence of iMRI guidance on the extent of resection and survival of patients with glioblastoma (GBM). METHODS: We analyzed data of all consecutive patients with GBM surgically undergoing complete tumor resection in our department between October 2007 and September 2009. All patients had a preoperative KPS of 70 or greater. The extent of resection was assessed on a 3-monthly basis. An independent neuroradiologist, blinded for the surgical treatment modality, assessed MRI data to determine the extent of resection. It was classified as complete if no, and incomplete if any residual contrast enhancement was detected on early postoperative MRI. RESULTS: Of the 101 patients meeting the inclusion criteria, 87 had a primary and 14 had a secondary GBM. Overall, the extent of resection was complete in 68.3% and incomplete in 31.7% of cases. Intraoperative MRI guidance was used in 28 patients. In 7 of these patients (25%), intraoperative imaging depicted residual enhancing tissue leading to further tumor resection. In the iMRI group, a complete resection was achieved in 25 patients (89.3%) compared with 43 (60.3%) in the conventional group (P < .01). Mean age was 55.8 years, which did not differ between the iMRI guided and conventional microsurgery group (54.9 vs 56.2 years, P = .8). Until March 1, 2010, 25 patients have died. Mean follow-up was 50.5 weeks. Kaplan–Meier estimates rendered a mean overall survival of 91.1 weeks. There was no statistically significant difference between patients with primary vs secondary GBMs (P = .5). Young age (P < .01) and complete resection (P < .05) were associated with a better outcome. CONCLUSION: Even in dedicated centers, intended radiologically complete tumor resections cannot always be achieved in GBM surgery. In terms of extent of resection, the use of iMRI improves the surgical success rate compared with conventional microneurosurgical techniques. These results need further confirmation by a randomized trial.

P.162. DELIVERY OF WHOLE CEREBRO-SPINAL AXIS (CRANIOSPINAL) RADIOTHERAPY USING A SUPINE, INVERSE-PLANNED INTENSITY-MODULATED RADIOTHERAPY (IMRT) TECHNIQUE: CLINICAL EXPERIENCE IN 16 PATIENTS
P. Whitehurst, J. Stratford, C. A. McBrain, C. Rowbottom, and R. Gattamanaeni; The Christie NHS FT, Manchester, UK

BACKGROUND: A new technique using inverse-planned IMRT to treat the whole CNS in a supine position was introduced into routine clinical practice in 2008. Initial technical and clinical experience is described. METHODS: Sixteen patients have been treated: medulloblastoma (7 patients), supratentorial PNET (5), ependymoma (3), and germ cell tumor (1). Median age was 18 years, range 8–49, 5 patients were <16. Treatment was planned using PHILIPS Pinnacle3 IMRT software and delivered in a head-first supine position. Pediatric patients required 2 isocenters (cranial-spinal junction) and adults require 3 isocenters (cranial-spinal and spinal junction). Staggered isocenters were incorporated into a single inverse IMRT plan, so that one standard daily set-up was employed throughout treatment. Clinical target volume (CTV) was defined as primary tumor volume (PTV) margins were 0.5 cm (cranial) and 1.5 cm (spine). Median prescribed dose was 35 Gy in 20 fractions to whole CNS, with the whole tumor boost (WBT) of 20 Gy in 10 fractions. Verification was performed with cone beam (XVI) imaging daily for fractions 1–3, then weekly, using an off-line no action level (NUL) protocol. Dose delivered to the CTV was assessed via direct recalculation of the plan on the XVI images. RESULTS: All patients completed treatment with acceptable toxicity. The use of a single plan significantly reduced complexity of treatment set-up and delivery. The use of inverse IMRT improved PTV conformity and minimized dose to OARs. Dose homogeneity was comparable with a posterior wedge pair technique and improved compared with a single posterior field. Uniformity of dose across the cranial and spinal junctions was also improved. Data quantifying these findings will be presented. Cone beam imaging allowed increased visualization and quantification of positioning including rotations. Although routine use of XVI highlighted discrepancies in the AP direction in the lumbar spine, all fields were delivered within the planning margins employed, following a systematic correction protocol. CONCLUSIONS: Introduction of an inverse-planned IMRT technique to deliver craniospinal radiation with a single plan in a supine position resulted in increased dose homogeneity and minimized dose to OARs, with improved workflow and reduced risk of operator error. Routine use of on-treatment XVI ensured that set-up corrections were employed only when there was a risk of CTV compromise. Scope to reduce CTV–PTV margins is being investigated.

P.163. MEDULLOBLASTOMA IN ADULTS: LONG-TERM SURVIVAL AND TOXICITY IN 47 PATIENTS TREATED WITH SUPINE WHOLE CEREBRO-AXIS (CRANIOSPINAL) IRRADIATION
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BACKGROUND: Since 1972 craniospinal irradiation (CSI) at The Christie has been delivered supine with a parallel pair of cranial fields and matching posterior wedge pair fields to the spine. This is delivered conventionally to reduce the dose to the thyroid, heart, and gonads. We report the survival and late effects of all adult medulloblastoma patients treated between 1980 and 2007 with this technique. METHODS: Medical records of patients ≥16 years old treated for medulloblastoma were analyzed retrospectively. Prescribed CSI doses were in 20 fractions with a primary tumor boost of 20 Gy in 10 fractions. Ten-to-twenty-gray boost was given to metastases. Kaplan–Meier method was used to calculate overall survival (OS), time to relapse and relapse-free survival (RFS). RESULTS: Forty-seven patients were identified (19 females, 28 males). Median age was 25 (range 16–56). Twenty-two patients had MRI staging, 2 had myelograms, and 4 were metastatic at diagnosis. Surgery was complete in 8 patients, subtotal in 36, and 3 had biopsy only. Median time from surgery to RT was 33 days (range 11–207). Forty patients received 30 Gy to CSI, 5 received 35 Gy, and 2 received <30 Gy. Three had concurrent vincristine only, 3

NEW DEVELOPMENTS IN RADIOTHERAPY

EXPERIENCE IN 16 PATIENTS

The Christie NHS Foundation Trust, Manchester, UK

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had concurrent vincristine and maintenance chemotherapy with CCNU and cyclosporin. Median follow up is 12.2 years. Nineteen of 47 relapsed (6 outside the radiotherapy treatment fields). Longest interval to relapse was 10 years. Five of 19 patients who relapsed are alive and in remission. The 5-, 10-, and 20-year RFS are 61%, 52%, and 49%, and OS are 68%, 52%, and 43%, respectively. At last follow-up 27 live independently, 11 are employed, 9 are married, and 3 (2 males, 2 females) have had children post treatment. All relapsed patients have undergone magnetic resonance imaging and needed hormone replacement treatment (3 growth hormone, 1 thyroxine, and 1 hydrocortisone). One patient developed epilepsy, 5 hearing impairment, and 2 second malignancies (breast, prostate). None developed meningioma, thyroid malignancies, or secondary BC. Six patients were noted. CONCLUSION: We report the longest follow-up data in adult medulloblastoma treated with a supine conformal radiotherapy technique. Our series is one of the largest and demonstrates survival comparable with published literature. Supine CSI is well tolerated by patients and reduces the long-term sequelae on the heart, thyroid, and gonads.

P.164. BORON NEUTRON CAPTURE THERAPY (BNCT): CLINICAL OPTIMIZATION OF UPTAKE PARAMETERS OF BORONOPHENYLALANINE (BPA)

D. G. Ngoga1, G. Cruickshank1, A. Detta1, S. Green1, N. D. James2, P.164. BORON NEUTRON CAPTURE THERAPY (BNCT): CLINICAL OPTIMIZATION OF UPTAKE PARAMETERS OF BORONOPHENYLALANINE (BPA)

INTRODUCTION: MGMT studies have demonstrated that a limited number of patients with glioblastoma benefit from Temozolomide. The remainder of the patients depend on radiotherapy at a maximum radiation dosage of 60 Gy, with no safe means of dose escalation. Boron neutron capture therapy (BNCT) is a binary treatment modality which represents a biologically targeted means of radiation dose escalation targeting both cycli-

cal and non-cyclical glioma cells1 without precluding other therapies. METHODS: We report on a Cancer Research UK clinical pharmacokinetic study of Boronophenylalanine (BPA) in patients with high-grade glioma to optimize uptake parameters for clinical trials of BNCT.

The goals of the study were:

• to investigate the pharmacokinetic profile of BPA in the new mannitol-based formulation;

• to evaluate the toxicity profile of BPA–mannitol; and

• to optimize the dose and uptake parameters for BPA–mannitol for use in future clinical trials of BNCT by integrating the tumor-handling data based on LAT-1 distribution and activity into the final pharmacokinetic model for clinical studies.

The study investigates the route of infusion and, in each case, will assess the effects of the administration of mannitol as a blood–brain barrier disruption. Measurements were made by Inductively Coupled Plasma Mass Spectrometry (ICP-MS) of 10B concentration in blood, urine, extra-cellular fluid (via brain macrodialysis), brain tissue around tumor and tumor tissue. Additional analysis was performed using Secondary Ion Mass Spectrometry (SIMS). RESULTS: Peak Boron (10B) levels in blood were in some patients until as late 6 hours after infusion, later than previously published data but were significantly enhanced by the addition of mannitol. Tumor concentrations were variable, reflecting the heterogeneity of glioblastoma. Peak concentrations were not achieved in some patients until as late as 6 hours after infusion, later than previously shown. This peak concentration correlated with concentrations in extracellular fluid. Administration via the intra-arterial route enhanced the tumor concentration, peaking 2 hours after blood BPA levels. CONCLUSIONS: Previous clinical studies into BNCT for glioblastoma have instituted early boron loading. Tumor resection was performed under speech and motor surveillance. All patients underwent MRI with neuronavigation and when possible 3. T. M. T. Scheper3, O. Vickerman3, V. Loky4, S. E. White5, G. Crosswell5, R. Sugar6, and A. Boddy7; 1University Hospitals Birmingham, Birmingham, UK; 2University of Birmingham, Birmingham, UK; 3CR-UK Formulation Unit, University of Strathclyde, Glasgow, UK; 4Regional Laboratory for Toxicology, Sandwell & West Birmingham Hospitals Trust, Birmingham, UK; 5Surface Analysis Research Centre, The University of Birmingham, Birmingham, UK; 62-hour blood BPA levels. CONCLUSIONS: The conformality index was much improved with RapidArc (typically 1.5 with conventional and close to 1 with RapidArc). Conformality was further increased by the use of manitol. Maximum doses to nearby critical structures such as optic nerves and optic chiasm were reduced with the use of RapidArc. There was a reduction in the volume of normal brain receiving a high dose. As these gliomas were within the temporal lobe, the ipsilateral hippocampus was within the PTV, so dose could not be reduced. Dose to the contralateral hippocampus varied from patient to patient. In some the contralateral hippocampus, dose was larger than the increased volume receiving low doses with RapidArc.

CONCLUSION: RapidArc is effective at reducing dose to OAR near to the PTV, improving conformity and reducing the volume of normal brain receiving a high dose of radiation in patients with temporal lobe gliomas. The use of RapidArc to improve conformity does not lead to hippocampal sparing per se. If low dose to the hippocampi is thought to be relevant to long-term cognitive function, these organs need to be regarded as dose-limiting structures.

MISCELLANEOUS

P.166. AWOKE SURGERY DURING RESECTION OF INSULAR GLIOMAS

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PURPOSE OF THE STUDY: Insular gliomas are by many still considered inoperable, because of anatomical localization, vascular supply, and the potential devastating complications. We present our experience with the operative treatment of patients with insular gliomas in an “awake craniotomy” setting. PATIENTS AND METHODS: Nineteen consecutive patients with an insular tumor were operated during the period 2003–2009. Pre-operatively, an extensive neuropsychologic/linguistic workup was performed. All patients underwent MRI with neuropsychography and when possible fMRI. After cortical stimulation, the Sylvian fissure and perinsular sulci were opened. Tumor resection was performed under speech and motor surveillance. RESULTS: The patients average age was 41.4 ± 10.3 years. Pure insular lesions were found in 2 patients, a medial temporal base-insular glioma in 1, insular fronto-opercular and orbitofrontal-insular-temporal polar in 6 and 10 patients, respectively. Presenting symptoms included epilepsy (95%), dysphasia (26%), and cognitive problems (26%). In 13 patients, the resection was near total (95–98%) and <95% in the remaining 6 patients. Histology confirmed 16 low-grade and 3 high-grade gliomas. The average follow-up was 2.1 ± 1.5 years. Perioperatively 9 patients clinically deteriorated. However, all patients with a low-grade glioma recovered to preoperative status. Two patients with a high-grade glioma have died during follow-up.

CONCLUSION: Insular glioma surgery, facilitated by (sub)cortical stimulation in an awake setting, is feasible to acquire maximal cytoreduction in a safe manner. A dedicated surgical team is required, next to neurosurgeon, anesthesiologist, and patient interaction.
Most reported radiation-induced osteosarcomas arise from the facial bone or paranasal sinus after radiotherapy for retinoblastoma and/or pituitary adenoma. We report 2 radiation-induced osteosarcoma cases occurring in the paranasal sinus after treatment for frontotemporal glioma. CASE 1: A 56-year-old female underwent surgical resection of a left frontal tumor 16 years earlier in October 1990. The histological diagnosis was a low-grade glioma. In September 2006, a CT showed an osteolytic mass in the right frontal region. CT demonstrated an osteolytic mass in the left frontal and ethmoid sinus, a secondary operation was performed and the histological diagnosis was radiation-induced osteosarcoma. Radiotherapy was re-administered, but the patient died of rapid tumor re-growth. Radiation-induced osteosarcoma appeared 16 years after radiotherapy in Case 1, and 12 years after radiotherapy in Case 2. Given that the prognosis of radiation-induced osteosarcoma is poorer than that of primary osteosarcoma, careful attention is needed in considering the long-term survival of patients with glioma.

INTRODUCTION: Cerebral (venous) sinus thrombosis (CVST) in cancer patients is a rare complication, accurately diagnosed by MRI and MR venography (MRV). It has multiple etiologic factors with variable symptoms and signs at presentation and often with unpredictable outcome. We represent a young patient with metastatic germ cell tumor and a complication of CVST with good outcome. CASE REPORT: A 27-year-old male patient with primary retroperitoneal nonseminomatous germ cell tumor and metastases in the mediastinal and left scl lym nodes and bone (L3, direct extension from retroperitoneal mass) was admitted for initial chemotherapy (CTh). A week after the completed first cycle of CTh according to BEP (bleomycin, etoposide, cisplatin) protocol, the patient returned complaining of fever, nausea, and vomiting, with increased urinary output and melena. In admission, the patient had afebrile neutropenia, without clinical or laboratory signs of infection. During diagnostic procedures, urgent CT of the head disclosed no abnormalities, while MRI revealed a cortical thickening of both parietal and right frontal regions without any contrast enhancement or signs of expansion. Signs of CVST and cortical venous thrombosis were found retrospective on CT and MR images. EEG showed diffuse slowing down of background activity and focal slow-wave activity over the right frontal region. EEG findings were compatible with the signs of diffuse encephalopathy or encephalitis accentuated over the right frontal region. Diagnostic tests for excluding other causes of the condition, such as progression of malignant disease, metabolic, toxic, infectious and immune causes, were performed. After a few days, repeated MRI with inflammation, DW MRI, spectroscopy, and MRV disclosed focal changes in the frontal-parietal regions with surrounding edema containing white matter. MRI findings were compatible with the signs of venous sinus thrombosis of the right transversal sinus and partial thrombosis of the sigmoid sinus. The patient died of sepsis and already partly hemorrhagic cortical infarcts. After symptomatic treatment with antiepileptics and low-molecular-weight heparin, the patient slowly improved, and so did MRI findings. He continued with initial cisplatin-based CTh. After complete regression of mediastinal and retroperitoneal masses, the patient was admitted for second cycle of CTh with hypercoagulability and dehydration. Although this complication of CVST in the presented patient was probably related to cancer and the use of chemotherapeutic agents, the diagnosis of CVST was not considered. We report a case of CVST in a young patient with metastatic germ cell tumor and a complication of CVST with good outcome.

INTRODUCTION: Complementary and alternative medicines (CAM) are known to be used by cancer patients, but whether patients are fully aware of the therapeutic aspects of care. However, paradoxically, there are few specialist radiographers in this discipline. At the Beatson West of Scotland Cancer Centre, we examined the patient treatment pathway and key elements were identified where the input of a dedicated Radiographer was felt to be of benefit to our patients. OBJECTIVE: To evaluate the outcomes and the benefits of an integrated role for a Radiographer within a Neuro-Oncology team, given that radiotherapy remains central to the management of most brain tumors, the knowledge and skills incumbent in a radiographer’s role place them in an ideal position to manage many of the radio-therapeutic aspects of care. However, paradoxically, there are few specialist radiographers in this discipline. At the Beatson West of Scotland Cancer Centre, we examined the patient treatment pathway and key elements were identified where the input of a dedicated Radiographer was felt to be of benefit to our patients. OBJECTIVE: To evaluate the outcomes and the benefits of an integrated role for a Radiographer within a Neuro-Oncology team, given that radiotherapy remains central to the management of most brain tumors, the knowledge and skills incumbent in a radiographer’s role place them in an ideal position to manage many of the radio-therapeutic aspects of care. However, paradoxically, there are few specialist radiographers in this discipline. At the Beatson West of Scotland Cancer Centre, we examined the patient treatment pathway and key elements were identified where the input of a dedicated Radiographer was felt to be of benefit to our patients. The role of the Clinical Nurse Specialists (CNS) is well established in Neuro-Oncology teams, given that radiotherapy remains central to the management of most brain tumors, the knowledge and skills incumbent in a radiographer’s role place them in an ideal position to manage many of the radio-therapeutic aspects of care. However, paradoxically, there are few specialist radiographers in this discipline. At the Beatson West of Scotland Cancer Centre, we examined the patient treatment pathway and key elements were identified where the input of a dedicated Radiographer was felt to be of benefit to our patients. ELEMENTS: Elements were prioritized for introduction and protocols created incorporating ongoing assessment of competencies. The fundamental aspects of the Sp Rad role were identified early and quickly established: patient education regarding the process and delivery of radiotherapy; on-treatment assessment and management of toxicity; treatment verification with portal image review after training in anatomy recognition; and managing setup and immobilization issues for individual patients. More specialized tasks were gradually introduced, including identification and voluming of initially OAR’s then tumor volumes on the radiotherapy planning system (with subsequent checking by the neuro-oncology consultant); also a protocol was developed establishing CT-MR fusion for all Gloma patients receiving radical radiotherapy. The Sp Rad played a pivotal role in the development and implementation of the stereotaxy service and delivery of IMRT for selected glioma patients. The Sp Rad was instrumental in the drafting of clinical protocols (compliant with BMEIR regulations) and related quality documentation for both of these technologies. The Sp Rad was also responsible for delivering a training package for radiographers and assessment of competence. The Sp Rad is currently the lead coordinator for radiography services, liaising with the various diagnostic (MR) and therapeutic departments (simulation, planning, therapy delivery) as well as the patient to ensure rapid and efficient treatment delivery. The Sp Rad has been involved in other areas of service development, in particular creating a Pre-Treatment Assessment Clinic (PTAC), promoting working with the CNS. The PTAC addresses the increasing complexity of
multi-modality therapy facing most glioma patients, including issues of patient and carer education, psychological adaptation, symptom control, the ongoing appropriateness of the therapeutic strategy, detailed planning and preparation for treatment, and obtaining informed consent. Objectives include forging closer ties with the physics department to develop stereotactic IMRT, and supine craniospinal therapy delivery.

**P.171. CRANIAL BASE PARAGANGLIOMAS: GAMMA-KNIFE RADIOSURGERY**

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**INTRODUCTION:** Paragangliomas are highly vascular neuroendocrine tumors, usually benign and well encapsulated. In their cranial base location, microsurgery is associated to high morbidity (50%–80%) especially in relation to low cranial nerve damage. Gamma-knife treatment is emerging as a definitive therapeutic option in the treatment of these lesions. **MATERIALS AND METHODS:** We present a series of 57 patients bearing cranial base paragangliomas treated with Gamma-knife radiosurgery from February 1995 to January 2010. Forty-seven patients with a follow-up exceeding 2 years are analyzed in detail. There were 15 males and 42 females, with a mean age of 53.7 years (range 19.9–82.3). In 31 cases, there was a neuroimaging diagnosis exclusively, the other 16 had been operated and had a pathologically confirmed diagnosis. In the surgical group, 3 patients had their lesions previously embolized, and 2 had received fractionated radiotherapy while in the nonsurgical group 3 had received endovascular treatment, and 1 had fractionated radiotherapy. At the time of treatment, 6% of the operated patients were asymptomatic, and 81% and 94% had low cranial nerve and VIII cranial nerve deficits, respectively. In the nonsurgical group, 3% were asymptomatic, with low cranial nerve involvement in 74%, and 71% and 23% with VIII and V, VI, or VII cranial nerve deficits, respectively. The mean tumor volume was 14.2 cm³ (1.4–62.2 cm³), with a mean marginal dose of 13.6 Gy (12–15 Gy) and maximal doses between 20 and 55 Gy. **RESULTS:** Mean follow-up was 65.5 months (12–175). Volumetric control was obtained in 93.6%, (reduction in 68.1% and stabilization in 25.5%). Tumors progressed in three cases (6.4%). The volumetric reduction ranged from 0.75% (5%) to 15.35% (60%) (mean 5.6 cm³, median 3.4 cm³). No clinical complications were observed. **CONCLUSIONS:** Gamma-knife radiosurgery is an effective, safe, and efficient therapeutic option in the treatment of these tumors, as a first-line treatment or associated to surgery, endovascular treatment, and/or conventional fractionated radiotherapy.

**P.172. GAMMA-KNIFE RADIOSURGERY IN NEUROFIBROMATOSIS TYPE 2 (NF2) PATIENTS**

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**INTRODUCTION:** NF2 is an autosomal-dominant genetic disease with an incidence of 1 in 30,000 births and a prevalence of 1 case in 150,000 inhabitants. It is characterized by the simultaneous or consecutive development of intracranial or spinal meningiomas or schwannomas. The presence of bilateral VIII cranial nerve schwannomas is a main feature, with high surgical risks of cranial nerve deficits. **OBJECTIVE:** Analysis of our results of Gamma-Knife Radiosurgery in this group of patients. **METHODS:** Between March 2008 and April 2008, 70 treatments in 33 NF2 patients have been performed, 13 patients were treated in more than one occasion (1–4 treatments, mean 1.6). Seventy-eight percent of patients have a complete follow-up. Two-thirds were females. The mean age was 36.3 (12–79). Four patients had been previously operated (mean surgical procedures: 1.8 range: 1–4) and 22 had received previous radiotherapy. The mean number of treated lesions in one procedure was 3.9 (1–18), with a mean marginal dose of 12.7 Gy and a mean treated volume of 10.4 cm³. There was a known family history for only one-third of patients. **RESULTS:** The mean follow up time was 4 years (5–188 months), with 20% of patients followed for more than 5 years. The local volumetric control was obtained in 72.8% of cases with reduction in 31%. One hundred and forty-nine meningiomas and 62 schwannomas were treated. In 15 cases, the treated lesions grew (12 schwannomas and 3 meningiomas). In 39 cases, new tumors appeared during follow-up. From a clinical point of view, 28 patients remain stable, in 5 their symptoms improved and, in those where there was a clinical deterioration, hearing worsened in 11 cases. Three patients died as a result of progression of NF2. **CONCLUSIONS:** Gamma-Knife radiosurgery is an effective option to surgery in the treatment of NF2 patients, because of the minimal peripheral irradiation of healthy tissues, especially in meningiomas of patients previously operated on or with contraindications. Gamma-Knife Radiosurgery is an effective and safe, and efficient therapeutic option in the treatment of NF2 patients, because of the minimal peripheral irradiation of healthy tissues, especially in meningiomas of patients previously operated on or with contraindications.

**P.173. EXPLORING A NEW THERAPY FOR NEUROBLASTOMA: SILENCING OF DOUBLETROUBLE-LIKE KINASE USING RNA-INTERFERENCE**

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**Neuroblastoma** is one of the most common childhood cancers. Microarrays, protein profiling, and RNA interference agents are used in the treatment of these tumors. However, resistance to chemotherapeutic agents and systemic toxicity make neuroblastoma a difficult drug target. In our previous work, we found that doublecortin-like kinase (DCLK) gene transcripts are crucial mediators of associated proteins and correct proliferation and differentiation of neuroprogenitor cells. Gene expression profiling revealed a high expression of these transcripts in neuroblastomas and also in gliomas. Furthermore, these transcripts are endogenously expressed specifically in neuroblasts, but are not found in other cell types. Suppression of DCLK by short-interfering RNA (siRNA) disrupted the mitotic spindles in neuroblastoma cells and gene expression profiling revealed numerous differentially expressed genes indicating apoptosis. Apoptotic cell death of neuroblastoma cells by DCLK knockdown was further confirmed by several assays. Interestingly, mitochondria were the most affected cell components after DCLK long knockdown. We also found in human neuroblastomas a significant correlation between DCLK expression and genes related to mitochondria activity. Furthermore, we showed a successful delivery of siRNA-targeting DCLK to neuroblastoma cells by using specific peptide-RNA conjugates. In conclusion, silencing of the DCLK gene by siRNA interference is a novel potential therapeutic approach for neuroblastoma with the promise of combining high specificity with fewer side effects. Peptide–siRNA conjugates might be the tool needed for specific neuroblastoma delivery.

**P.174. USE OF SHORT BATTERY FOR COGNITIVE, ANXIETY, DEPRESSION, AND QUALITY OF LIFE EVALUATION (BATCOG) IN PATIENTS WITH GLIOMAS: A FEASIBILITY STUDY**

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**INTRODUCTION:** Cognitive difficulties (CDs) are very common in patients with gliomas, and their origin is multifactorial: tumor, surgery, radiotherapy, chemotherapy, antiepileptic drugs, steroids, and anxiety and depression are commonly described factors. However, the prevalence of CD is difficult to estimate. Disparities among studies are frequently explained by methodological differences. Performance status scales (KPS, ECOG) and short screening tests for CD (MMSE, MDPS) have a low sensitivity and specificity to detect CD in patients with gliomas, particularly in those with mild impairment and/or high premorbid function. A better approach is to use a battery of tests directed to evaluate the cognitive domains more frequently impaired in these patients. **METHODS:** Patients with primary brain tumors and CD were recruited from the Neuro-oncology Clinic. All subjects were evaluated with a selected battery of tests that examine the cognitive domains more frequently affected by cancer and its treatment (attention, memory, and executive function); similar batteries have shown usefulness to evaluate cognitive function in patients with gliomas. Tests are standardized for Spanish population. A screening test for anxiety and depression and a quality of life tool were also included. The battery comprises: Rey Complex Figure Test, Word list (WMS-III), Digit-Span Test, Symbol Digit Modalities Test, Trail Making Test A&B, FAS, STROOP, HADS, and EORTC QLQ-C30. **RESULTS:** A total of 7 patients were evaluated up to now. Median age was 43.5 years (28–68); 2 were men and 5 were women; all patients had at least primary studies. Tumor diagnosis was grade III glioma (2), grade II glioma (1), and meningioma (1). Test results show more deficits in delayed...
recall, working memory, mental flexibility, and verbal fluency compared with normalized population, in the absence of anxiety or depression. Completion time test was ~1 hour. Recruitment of further patients and a control group matched by age, sex, and level of education is currently ongoing. CONCLUSIONS: The introduction of a battery of cognitive tests for cognitive and quality of life evaluation was feasible and well accepted by patients. This experience will serve as a basis for future development of cross-sectional and longitudinal studies of cognitive function and quality of life in patients with gliomas in our environment. There is a need for specialized neuropsychological assessment in neuro-oncology patients.

P.175. A LITERATURE REVIEW OF FIBRO-OSSEOUS PSEUDOTUMOR: THE ROLE OF SURGICAL EXCISION
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BACKGROUND: Fibro-osseous lesions are a rare clinical entity. We present the case of a 63-year-old female with infrequent partial seizures. Electroencephalography revealed Grade I dysrhythmia of the right hemisphere and an MRI revealed a calcified lesion in the right precentral frontal lobe. The patient underwent surgical resection and histopathology revealed a fibro-osseous pseudotumor. No further treatment was required and the patient is symptom-free 1-year post-operatively. METHODS: A review of all existing cases of fibro-osseous lesions was undertaken. The clinical and radiographic characteristics, histopathology, management and outcome of each case were evaluated. The suspected pathophysiology of these lesions was reviewed. RESULTS: Only 44 cases (28 intracranial, 16 spinal) have been reported to date. The majority occur in adults over 40, with a slight male predominance. Neurological symptoms result from local mass effect; however, seizures are also frequently observed. Imaging demonstrates central calcification with variable contrast enhancement. Histopathologically, a variably calcified chondromyxoid matrix with surrounding glial and without mitoses or cellular atypia is characteristic, suggesting a reactive origin to the lesion. In all reported cases, surgical excision is curative with only one reported case of recurrence. No further treatment is required, although routine surveillance may be of benefit. CONCLUSION: Although uncommon, awareness of this entity and its inclusion in the differential diagnosis of long-standing calcified lesions along the craniospinal axis has practical importance in preventing unnecessarily aggressive investigation and treatment.

P.176. INVESTIGATION ON THE INCIDENCE, PREVALENCE AND MORTALITY RATE IN FIVE CITIES/DISTRICTS IN EASTERN AND NORTHERN CHINA
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PURPOSE: To provide accurate, population-based incidence rate, prevalence rate, and mortality rate of primary brain tumor in the Chinese population. METHODS: We investigated 5 big communities in China. They were Baoshan district of Shanghai city, Long-nan district of Daqing city, Ma’anshan city, Shi-yan city, Pu-yang city. The incidence, prevalence, and mortality rates from October 1, 2003 to September 30, 2006 were measured. RESULTS: The incidence rate, prevalence rate, and mortality rate of primary brain tumors in the investigated areas were 10.5/100,000, 24.5/100,000, and 4.3/100,000 respectively. Among males, these rates were 8.3/100,000, 20.3/100,000, and 3.6/100,000 respectively, and for females, 12.8/100,000, 29.0/100,000, and 5.1/100,000. The incidence rate for glioma was 3.13/100,000. CONCLUSIONS: This is the first report on the incidence rate and prevalence rate of primary brain tumors in China. Further study on the different histological subtypes and the etiology and risk factors of brain tumors are warranted.
pellets. For 3 individual patient series, we analyzed for copy number aberrations (CNAs) on Affymetrix SNP 6.0 arrays. RESULTS: In 12 months, a total of 59 glioma samples were collected; of which, 31 (52%) were propagated successfully. The success rate of SS cultures was solely dependent on the tumor size whereas the success rate in SF cultures was dependent on both sample size and initial amount of NS formation. SF tumor neurosphere cultures could be successfully transferred to monolayers in 96-well plates by seeding the cells on growth factor-reduced ECM coating, thereby attaining a model for drug screening. Successfully propagated tumors had similar genetic aberrations as the primary tumor. Genetic aberrations include high copy amplification of Chr.7p11 (EGFR) and loss of Chr. 9p (CDKN2A) and Chr10, all of which are common genetic aberrations in gliomas. Some CNA became more apparent in SF cultures through selective clonal expansion. Importantly, SS cultures showed a gradual loss of CNAs in higher passages.

CONCLUSIONS: We developed an efficient protocol for SS and SF culture derivation of surgically removed tissue. Using growth-factor reduced ECM coating, we are able to culture monolayers of GBM cells under SF conditions, which allows high throughput screening of patient-derived tumor cells with genetic profiles resembling the parental tumor up to high passages. However, the lower success rate of obtaining viable SF cultures remains a disadvantage. Moreover, we have determined the genetic aberrations of SS cultured material to be similar to tumor tissue in low passages (up to p4). This is, for practical and financial reasons, an attractive option next to SF cultures.

P.179. IDENTIFICATION OF MAGNETIC RESONANCE IMAGING SURROGATES FOR GLIOMA GENE-EXPRESSION MODULES
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OBJECTIVE: To combine magnetic resonance imaging with microRNA detection and analysis to create a multidimensional map of gene-expression patterns in glioblastoma multiforme (GBM) that provided clinically relevant insights into tumor biology. METHODS: Eighty cases of GBM were studied. Tumor contrast enhancement and mass effect predicted activation of specific hypoxia and proliferation gene-expression programs, respectively. In total, 1147 miRNA were detected and analyzed. RESULTS: The relationship between MRI phenotype and the respective gene-expression profiles were identified. MiR-21, MiR-181, and MiR-221 were found related to tumor infiltrative. CONCLUSION: An in vivo portrait of genome-wide gene expression in GBM offer a potential strategy for noninvasively selected patients who may be candidates for individualized therapies.

P.180. A NOTE-BASED STUDY OF HOW PATIENTS FIRST PRESENT WITH PRIMARY BRAIN TUMORS
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INTRODUCTION AND OBJECTIVES: GP guidance on the presenting symptoms of brain tumors is based on data sourced from tertiary care centers. As GPs will see, on average, only 4 patients with a new primary brain tumor during their career, they are reliant on these guidelines rather than experience. Small selective studies by Salander and Davis on early symptoms show a difference between reported initial symptoms and the symptoms at confirmed diagnosis. By collecting data on the presenting symptoms of an unselected, prospectively defined population of patients with incident brain tumors we aim to refine the guidance. METHODS: From May 2009, data were collected weekly from a neuro-oncology MDT meeting. The MDT supported a population base of ~3 million people (includes the following PCTs and district hospitals: Wandsworth; Frimley Park; East Surrey; Sutton and Merton; Kingston; Richmond and Twickenham; Croydon). Information on the presenting complaint was recorded for those patients meeting the inclusion criteria. The patient inclusion criteria were the first occurrence of a subsequently confirmed adult primary brain tumor (gliomas and meningiomas) whether benign or malignant. The exclusion criteria: metastatic brain tumors; spinal cord masses; pituitary tumors; peripheral nerve tumors; those with a previous history of brain tumors; pediatric cases (age <16). RESULTS: Data were collected for 137 patients. Cognitive loss was the most frequently reported symptom (39%). The red flag symptoms of headache and seizures were reported by 28% and 18% of patients, respectively. Of the 39 patients who reported headache symptoms, 4 of these patients reported headache as their only symptom. CONCLUSION: This study shows that the current beliefs about “red flag” symptoms (headaches and seizures) for brain tumors in the primary care setting, which are based on tertiary care data, may not be the most commonly reported symptoms in the community. The preliminary data show that cognitive loss and weakness are more frequently reported, and that headache alone does not seem to predict diagnosis of primary brain tumor.