RESULTS: The tracer uptake ranged from faint to profound (mean L
Spearman’s rho analysis we found no correlation between tracer uptake (L
method of image analysis, calculating the lesion-to-normal (L
chemistry. Radiotracer accumulation was assessed by a semiquantitative

data suggest that99mTc-TF uptake is not influenced by P-gp expression in
females, mean age 57.3 years) with histologically confirmed glioma were
received radiotherapy (60 Gy in 30 fractions) with concomitant (75 mg
MR scan were selected from the neuro-oncology clinic, followed by
methods of patients with GBM. METHODS: All files of patients with GBM with
chemo-therapy alone, or on an investigational trial. Magnetic resonance
were treated with bevacizumab and a cytotoxic chemotherapy, cytotoxic
Treatment is challenging for conventional MR imaging (MRI). To
progression on bevacizumab did not differ by pattern of radio-
odified GBM at diagnosis manifest MRI-defined local disease and maintain this
(152 
P < 0.03). ASSESSMENT OF BEVACIZUMAB
IRINOTECAN IN RECURRENT GLOBLASTOMA
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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 disease and distant invasion as assessed radiographi-
cally. PATIENTS AND METHODS: 80 adult patients with glioblastoma
were treated with surgery followed by radiotherapy (RT) and concurrent
and adjuvant temozolomide (TMZ). 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 presen-
tation, first recurrence, second, and third recurrence. Four patterns of radiographic
disease were assessed, local (unifocal disease), distant (second lesion noncon-
tiguous 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 recur-
rence 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 radio-
graphic 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.

CONCLUSION: pMRI seems to be a reliable technique to distinguish PD from Pd-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 anti-
angiogenic 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 ultra-
structural 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 hyperen-
hancement nonenhancing 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 programs 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 268.5 (± 29.43) (P < 0.02) to 126.52 (± 29.43) (P < 0.01). In vitro
in vitro

cell line (10000 cells) and 7 days later, we harvested the cells for quantitative analysis. RESULTS: The model was able to predict the growth of the glioblastoma with a coefficient of determination (R²) of 0.85, indicating a high level of accuracy. CONCLUSION: The developed model provides a reliable tool for predicting glioblastoma growth, which could aid in the early detection and management of this disease.
DTI-fiber tracking (DTI-FT) allows the reconstruction of subcortical tracts and their relationship with tumors. This work assesses the ability of preoperative DTI-FT 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 cortico-spinal tract (CST), the internal fronto-occipital (IFO), and superior longitudinal fasciculus (SLF) fascicles were reconstructed by DTI-FT. 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. Intraoperative protocol included intraoperative language and motor mapping and monitoring (EEG, ECoG, EMG, and MEP). DTI-FT images were loaded into the neuronavigation system and available during surgery. Surgery was carried out according to standard clinical protocols. For each patient, preoperative and postoperative MR images and DTI-FT were loaded into the neuronavigation software and image fusion was used to evaluate the extent of resection as well as the correspondence between the resection boundaries and the preoperative DTI-FT. 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 tumors showed more than one tract infiltration. Tract infiltration was related to tumor location and volume, being more frequently observed in Rolandic and large tumors. When no tract infiltration was documented by DTI-FT, the extent of resection was total in all the cases. When one tract was infiltrated, extent of resection was total in 70% 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 was more frequently associated with a reduced chance of resection. Preoperative evaluation in DTI-FT of the level of CST and IFO were performed for the chance of performing a total resection. When CST and IFO are infiltrated by the tumor, a total removal is rarely possible; when were outside, an extensive resection is feasible. Preoperative DTI-FT 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: 1-L-[Methyl-11C]methionine (MET) positron emission tomography (PET), [18F]-fluoro-2-deoxy-2-fluoromethoxy (FDG) PET, and [11C]-fluoromisonidazole (FMISO) are sensitive modalities for visualizing primary brain tumor. In the current study, we investigated the usefulness of these modalities for the prediction of the extent of resection and the relationship 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 anaplastic astrocytoma, 1 glioblastoma, 1 oligodendroglioma, 1 anaplastic oligodendroglioma, and 22 glioblastomas), using MET-PET studies preoperatively. Moreover, 35 patients (17 males, 18 females; mean age: 51.4 years; range: 22–81 years; 6 diffuse astrocytomas, 1 anaplastic astrocytoma, 1 anaplastic oligodendroglioma, and 21 glioblastomas) were examined with FLT-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 (SUVM), 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 SUVM and and Ki-67 index were determined using spearman’s rank correlation test. 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 II and III gliomas. FLT SUVM in the tumor had a stronger correlation with Ki-67 index than MET SUVM. 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 imagining 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 GLIOBLASTOMA: A TRANSVERSAL 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 temozolomide. We 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 PMS2. METHODS: MGMT promoter methylation status was assessed in 818 primary and recurrent glioblastomas using nonquantitative methylation-specific PCR (MSP). The vital tumor cell content of each primary and recurrent tumor specimen was histologically determined. Quantitative promoter methylation analyses using DNA pyrosequencing of MGMT in 48 patients as well as for the DNA mismatch repair genes MLH1, MSH2, MSH6, and PMS2 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, borderline 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 reduced methylation of MGMT promoter was detected only 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 reduced protein levels and is apparently 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, 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
tumor resections (25 patients) and stereotactic biopsies (39 patients) were used for subsequent analyses. MGMT promoter methylation was determined by methylation-specific PCR (MSP). MGMT mRNA expression was analyzed by real-time qPCR and normalized against adequate housekeeping 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 < .0001). Conversely, un methylated 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 glioma patients undergoing chemotherapy. 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.09. UPDATED RESPONSE ASSESSMENT CRITERIA FOR HIGH-GRADE GLIOMAS (HGG): REPORT FROM THE RESPONSE ASSESSMENT IN NEURO-ONCOLOGY (RANO) WORKING GROUP M. van den Bent1, D. MacDonald2, S. Chang3, M. A. Vogelbaum4, and P. Y. Wen2; 1Daniel den Hoed Cancer Center, Rotterdam, Netherlands; 2London Regional Cancer Center, London, ON, Canada; 3UCSF, San Francisco, CA; 4Cleveland Clinic, Cleveland, OH; 5Dana Farber/Brigham and Womens Cancer Center, Boston, MA

Accurate determination of response and progression is crucial to evaluate new brain tumor treatments and care for patients. Macdonald’s criteria (Macdonald et al. J Clin Oncol. 1999; 8:1277–80), based on measuring cross-sectional enhancing tumor area, taking into account changes in steroid dose and neurological status, have been widely used. Limitations include difficulty in measuring tumors with complex shapes or indistinct borders, nontumor factors that produce imaging changes, reaction to local therapies, posttreatment changes that may mimic tumor, and lack of applicability to nonenhancing tumors. Anti-angiogenic therapies, which reduce MRI enhancement by restoring the blood–brain barrier, while nonenhancing tumor may enlarge, highlight the difficulty of assessing novel treatments. The RECIST criteria use unidimensional tumor measurements, do not consider steroids or neurological status, and have the limitations of Macdonald’s criteria. The RANO group is an ongoing unofficial international multidisciplinary consensus-building effort to develop new response criteria. The now published RANO criteria for HGG measure cross-sectional enhancing and nonenhancing tumor area, and account for the changes in steroid dose and neurological status (Wen et al. J Clin Oncol. 2010; doi: 10.1200/JCO.2009.26.3541). Within the first 12 weeks of completing chemo- radiation, progression requires either new tumor outside the high-dose radiotherapy field or biopsy-proven tumor, to avoid “pseudoprogression.” T2/FLAIR images receive more emphasis, particularly in trials on anti-angiogenic agents. Hind sight may allow a more accurate determination of progression and is now a formally described part of the outcome assessment procedure. Increase of steroids alone is still not perceived as sufficient evidence of progression.


In this trial, it was tested as a single modality in recurrent GBM, and compared with the best available chemotherapy. This treatment holds promise as monotherapy, has only very limited and local toxicity, and may be well suited for combination with standard chemotherapy.

O.11. STEM/PROGENITOR CELL FLEXIBILITY DETERMINES BOTH NORMAL BRAIN DEVELOPMENT AND BRAIN TUMORS P. Sathyam, M. Kamal, S. Singh, F. Robinson, and S. Majumder; University of Texas MD Anderson Cancer Center, Houston, TX

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, REST-silencing transcription factor (REST). REST is expressed in most neuronal cells, including neural stem/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, indicating that NSCs or PCV cell flexibility of stem/progenitor cells. Although REST is normally not expressed in most neural cells, we recently 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.
Abstracts

O.12. EFFICIENT ENGRAFTMENT OF MGMTP140K 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, but has associated with dose-limiting hematotoxicity. OBJECTIVE: To assess safety and efficacy of a retroviral vector encoding the O6BG-resistant MGMTP140K 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 bolus, then 30 mg/m2/d). RESULTS: The BCNU dose was nonmyeloablative with ANC <500/µL for ≤5 d and nadir thrombocyto-penia of 28,000/µL. Gene marking in pre-infusion colony forming units (CFUs) was 70.6%, 79.0%, and 74.0% in Patients 1, 2, and 3, respectively, by high-thru-PCR. Gene marking in white blood cells and sorted granulocytes ranged between 0.37–0.84 and 0.33–0.83 progenitor cells, respectively, by real-time PCR. Posttransplant gene marking in CFUs from CD34-selected cells ranged from 28.5% to 47.4%. Patients have received 4, 3, 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 7–8 months subsequent CONCLUSIONS: We believe that these data demonstrate the feasibility of achieving significant engraftment of MGMTP140K-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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Numerous molecular events have been described in the course of molecular progression, molecular malignancy being characterized by the cooccurrence of multiple changes and their exact malignant character (hemisomy, low-level gain (<20%), low-level loss (<10%), high-level gain (>25%), low-level loss (<10%), high-level loss (>10%), homozygous loss, low-level gain, low-level loss, high-level gain, and high-level loss). Interestingly, different types of 1p/19q aberrations were identified, some of them being indicative for molecular malignancy (partial or full losses) which warrants an accurate identification, separating them from those indicative of a favorable biological behavior (codeletion of complete 1p and 19q). We are currently evaluating the clinical relevance of identification of molecular malignancy as proposed, and preliminary results indicate that this scheme will be helpful for establishing a risk-profile for individual glioma patients and thereby ultimately aid in therapeutic decision-making.

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

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MGMT status is a predictive factor of response to standard treatment of newly diagnosed glioblastomas involving temozolomide (TMZ) and radiotherapy. It is used as a prognostic factor in newly diagnosed glioblastoma, being becoming a crucial biological marker in new clinical glioma trials, and is being used in routine clinical practice, there is a strong need to determine the best technique for MGMT analysis. In a French multicenter study, compared 5 techniques: classical MS-PCR, Methylight, pyrosequencing (PYR), MS-HPA, and immunohistochemistry (IHC). Each technique was centrally performed at an expert center. To analyze the reproducibility of MGMT methylation assays, 3 primary cell lines (GB2/GBM2) were tested in 10 separate series. GB2 and GB3 were never methylated (Meth) with either Methylight or MS-HPA, but were Meth in 7 of 10 and 9 of 10 cases with MS-PCR, respectively, while methylation levels were 5% and 9% for PYR, with reproducibilities of 11% and 6%, respectively. GB2 and GB3 were always Meth with MS-HPA and MS-PCR, methylation levels being 42% and 77% for Methylight and PYR, with reproducibilities of 72% and 72%, respectively. A good linearity was observed for each technique (after sequential mixing of 100% and 0% methylated samples) with detection of levels as low as 2.5%. For IHC, slides from two selected blocks were immunostained and analyzed in 6 different series. The number of positive cells ranged from 8% to 60% (mean 31%) in 1 case and from 3% to 20% (mean 8%) in the other. Followings tests on 99 samples from patients with newly diagnosed GBM treated with standard treatment (radiotherapy and TMZ), the best predictive values for overall survival were obtained by PYR (P < 0.001/cut off 9%), MS-PCR (P < 0.0001), and IHC (P < .001/cut off 25%). Methylight (P = .09) and MS-HPA (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.
of NDRG2 expression is found in several human cancer cell lines and tissues, including meningiomas and glioblastomas (GBs). AIM: A gene expression profiling analysis to identify differentially expressed genes between high- and low-grade gliodendrogliomas (OGs) revealed that NDRG2 was consistently down-regulated in high-grade OGs. Therefore, to analyze the potential role of NDRG2 as a TSG in gliomas, we performed mRNA expression and promoter hypermethylation of NDRG2 in a series of 78 primary glioma tumors, MATERIAL AND METHODS: The human glioma tissue samples comprised of 15 GBs (WHO grade IV) and 59 oligodendrogliomas (OGs), including 19 WHO grade II oligodendrogliomas (OGs), 16 WHO grade III OGs, 11 WHO grade II mixed oligoastrocytomas (OAs), and 13 WHO grade III OAs. mRNA expression levels were measured by quantitative real-time reverse transcription polymerase chain reactions (qPCR). Analysis of promoter hypermethylation was determined by sodium bisulfite-modified treated DNA followed by methylation-specific PCR. RESULTS: Low mRNA expression levels relative to non-tumoral brain tissue were detected in 50% (5 of 10) of high grade OTs, and 92.5% (12 of 13) of GBs. In contrast, only 7.1% (4 of 56) of low grade OTs showed NDRG2 reduced mRNA expression levels, Promoter hypermethylation was detected in 38.5% (10 of 26) of high-grade OTs, as well as in 58.8% (10 of 17) of GBs, while none of the low-grade OTs showed NDRG2 promoter hypermethylation. Likewise, there was a significant correlation between the low RNA expression levels and/or the promoter hypermethylated of NDRG2 in high-grade OTs through hypermethylation of its promoter region, which points out its role as a TSG. In addition, NDRG2 inactivation may be a useful biomarker to predict a more aggressive behavior in OTs.

O.16. A FOUR-GENE SIGNATURE ASSOCIATED WITH CLINICAL OUTCOME IN HIGH-GRADE GLIOMAS
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Molecular studies of high-grade gliomas (HGGs) have highlighted the heterogeneity of these tumors, and have linked molecular signatures to clinical outcomes. Moreover, the identification of metastatic cells that escapes from standard therapies. To identify such molecular subtypes of tumors is essential for guiding therapeutic advances. We report the development and validation of a robust risk-score model highly associated with the outcome of patients with newly diagnosed HGGs. We conducted a supervised approach to account for the WHO grade of malignancy when deriving gene biomarkers associated with outcome. We performed a meta-analysis of HGGs microarray data sets (267 patients) to identify such biomarkers from a robust signature related to tumor aggressiveness. These biomarkers were used to construct a risk-score model based on the model proportional Cox proportional hazard model. The model was associated with overall survival (OS) and with good discrimination (C-statistic) was based on the expression of 4 genes. Patients were ranked according to their risk score and stratified into 2 groups. Low-risk score patients had a median OS longer than high-risk score patients (46.6 vs 11.7 months, P < .001). These results were validated on an independent microarray study of 59 patients. We performed RT-qPCR validation on an independent set of HGGs (194 patients) and compared the performances of our risk-score model with the prognostic value of currently admitted clinical and molecular risk factors. Two multi-variate models were built, including age, treatment, grade, RTOG RPA classes, MGMT methylation status, and IDH1 mutational status; one with and one without the 4-gene expression risk score. These models were used to estimate the prognostic value of the gene expression risk score for 176 patients for complete data sets for all variables and for a subset of 105 patients treated with temozolomide chemoradiation. This additional analysis revealed that both the mutations of IDH1 and the presence of MGMT promoter methylation were associated with a survival benefit (P < .01 in the whole cohort and P < .05 in the subset). It also showed that the 4-gene risk score was strongly associated with OS in these two groups, independently from clinical and molecular risk factors (P < .01). Each time, the model discrimination improved significantly with the addition of the 4-gene risk score (0.816 vs 0.846, P < .001 and 0.792 vs 0.822, P < .001, respectively), showing that it added beyond standard clinical parameters and beyond both the MGMT methylation status and the IDH1 mutational status.

One explanation for the association between the 4-gene signature and clinical outcome is that it may detect the molecular fingerprints inherent to this group of tumors. These results suggest the importance of the 4-gene signature as a stratification factor for future comparative therapeutic trials, though it needs to be further investigated in a prospective clinical study.

O.17. EXPRESSION OF TELOMERASE REVERSE TRANSCRIPTASE (hTERT) IN HUMAN GLOBLASTOMA SPECIMEN IS ASSOCIATED WITH SHORTER PATIENT SURVIVAL AND IS A PREREQUISITE FOR IN VITRO IMMortalIZATION
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hTERT, the catalytic subunit of human telomerase, contributes to cancer cell immortalization by telomere stabilization. The aim of this study was to characterize hTERT expression in gliomas and the respective prono-cell cultures with a focus on glioblastomas (GBMs) and to investigate its role with disease progression in vivo and tumor cell immortalization in vitro.

Since 2001 primary cell cultures have been established from 272 tumor tissues histologically verified according to WHO criteria as low-grade glioma WHO I/II (n = 23) and anaplastic astrocytoma WHO III (n = 14), GBM WHO IV (n = 22), gliosarcoma (n = 7) and giant cell glioblastoma (n = 2). hTERT mRNA expression was investigated in all primary cell cultures and additionally in GBM tumors in 96 (by RT-PCR) and calculated relatively to GAPDH mRNA. Data were verified in subgroups by real-time RT–PCR. Telomerase enzyme activity was assessed using the Telomeric Repeat Amplification Protocol (TRAP) of the TRAPeze Telomerase Detection Kit (Chemicon), hTERT expression levels were compared with overall survival of GBM patients using SPSS software. Twenty-nine percent of the total culture population expressed hTERT. In the whole cohort, hTERT expression was associated with longer overall survival, showing that it added beyond standard clinical parameters and beyond both the IDH1 and IDH2 (mutations rate 36.6%) and only 35% of patients with hTERT expression. All long-term survivors (n = 13; >40 months) were low/negative with respect to both hTERT expression and the ability for extended in vitro cultivation. In parallel to prono-cell cultures, hTERT expression was analyzed in 96 GBM tumor samples. Forty-seven percent of the 96 samples (49%) showed detectable hTERT expression. Kaplan–Meier survival analysis showed a borderline significant survival benefit for patients whose tumors lacked hTERT expression with a median survival of 20.1 months vs 14.3 months for patients whose tumors expressed hTERT. All long-term survivors (n = 13; >40 months) were low/negative in telomerase. Summing up our data show that telomerase activity is essential for successful in vitro propagation of glioma cell models implicating that hTERT should be regarded as a prerequisite for tumorgenesis. Our results show that hTERT expression in the tumor tissue is associated with longer overall survival in glioma patients, indicating that hTERT might have quality as prognostic biomarker predicting tumor aggressiveness.

O.18. IDH1 MUTATIONS IN GLIOMAS: CORRELATION WITH GENOMIC PROFILE AND PROGNOSIS
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Recently, IDH1 codon 132 mutations (mostly Arg132His) have been found in gliomas, resulting in the loss of normal isocitrate dehydrogenase activity and the acquisition of an alpha-ketoglutarate reductase activity. Rarely mutations can also affect the mitochondrial isoform activity and the acquisition of an alpha-ketoglutarate reductase activity. Using direct sequencing and new PCR approaches such as COLD PCR (compaomilication at lower denaturation temperature–PCR) combined with high-resolution melting (HRM), we investigated the mutational status of IDH1 and IDH2 gene in 2272 gliomas and central nervous system including 1821 gliomas (1238 when considering initial surgery), all with a better outcome in grade II (143.0 vs 92.0 months, P < .001). IDH1 mutated on IDH1 (92%) or IDH2 (8%) mutations were inversely correlated with grade, affecting 234 of 347 (67%) grade II, 165 of 341 (48%) grade III, and 43 of 55 (8%) grade IV gliomas. IDH1 mutation was tightly related to the 1p19q codeleted group and MGMT methylation, but mutually exclusive with EGF amplification (2.5% IDH1 mutated 4 of 177). Strikingly, all the 1p19q codeleted gliomas were mutated on IDH1 (92%) or IDH2 (8%). IDH1 mutation was associated with a better outcome in grade II (143.0 vs 92.0 months, P = .002).
grade III (10.90 vs 20.0 months, P < .0001) and grade IV gliomas (27.0 vs 14.0 months, P = .0002). After adjustment for grade, age, MGMT status, genomic profile, and treatment, multivariate analysis confirmed that IDH status remains a favorable prognostic marker in the entire patient population of gliomas (HR = 0.6; 0.42–0.84). Then, combining innovative PCR approaches and biochemical dosages, we were able to determine the IDH status in the biological fluids of a subset of these patients. In order to determine whether IDH1 status may predict response to treatment, we are now investigating the response to radio- and chemotherapy of glioma cells expressing mutated vs wild-type IDH1. Updated results will be presented.

**BRAIN AND LEPTOMENINGEAL METASTASIS**

**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 carcinomatosis (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 was to present the preliminary results.

**RESULTS:** 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 score ≤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 chemotherapy with or without systemic chemotherapy. Univariate analysis identified female sex, breast cancer, Karnofsky Performance Status, negative CSF cytology, PI, and treatment (intrathecal chemotherapy), as independent good prognostic factors for overall survival. However, multivariate analysis revealed that breast cancer (HR: 3.03, 95% CI: 1.33–11.11, P = .031), negative CSF cytology on cerebrospinal fluid (CSF) or CSF biochemical abnormalities (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, neoplastic lymphocytes 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.

**PATIENTS AND METHODS:** To establish cytomorphological criteria, 42 cytopen preparations of CSF from patients with confirmed CSF involvement by aggressive lymphoma or acute leukemia were compared with 26 samples of inflammatory diseases. CSF cytology was analyzed morphologically for preselected parameters of cell, cytoplasm, and nuclei and the presence of mitoses or apoptoses. For the comparison of cytology and MRI we evaluated retrospectively for MRI signs of neoplastic meningitis and for CSF protein abnormalities (total protein, oligoclonal bands, lactate, and ferritin).

**RESULTS:** As expected, none of the cytomorphological parameters sharply discerns neoplastic and inflammatory changes. However, neoplastic cells were significantly larger than inflammatory lymphocytes with a mean of 3.0 as opposed to 1.8 times the size of normal small lymphocytes (P = .0001). Moreover, irregular shape, pointed borders of the cytoplasm, and deep notches in the nucleus were significantly more often found with neoplastic than with inflammatory lymphocytes. The total cell count was elevated in 68% of cases of lymphomatous meningitis. While cytomorphology was comparable with MRI in solid neoplasms, it could also achieve approximately 90% sensitivity for the detection of NM. In hematological neoplasms, spinal and/or cisternal MRI detected only 71% of cases with normal and 52% with elevated cell counts. Total protein was elevated in 77% of cases, lactate in 55%, and ferritin in 48%. Oligoclonal IgG was found in 11% isolated in the CSF and in 18% in CSF and serum identically. In approximately 95% of all cases of NM, at least one of the analyzed laboratory tests was pathological. **CONCLUSIONS:** CSF cytology is more sensitive than MRI for the detection of NM from hematological and comparable in solid neoplasms, but application of both methods clearly enhances the sensitivity by at least 10%. No single cytomorphological pattern is sufficient to detect neoplastic lymphocytes. Considering a combination of cell size and irregular shape of cell and nucleus may improve the diagnostic accuracy of CSF dissemination by aggressive hematological malignancies.

**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 salvage therapy for distant brain failures. We report our initial experience using a linac-based frameless radiosurgery system. 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 (ExacTrac by Brainlab) linear accelerator-based radiosurgery 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 3.1–12.1 months) 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 3 patients (1 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 0.31 mm). CONCLUSIONS: Frameless stereotactic radiosurgery to the postoperative surgery for a 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 MULTICENTRE BASE 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 the aim to assess if improvement in outcome could be achieved with any of the regimens. RESULTS: Fifty-nine patients (36 M, 23 F; 9 after primary chemo) were included. Median age was 61 years (range 46–82), WHO PS 0 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 histology. GFT arm was closed early after stage 1 analysis when the 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% [intracranial perforation (2 patients), pneumonia (2), pulmonary emboli (1), pneumothorax (1), seizure (1)]. We summarize here other patients’ characteristics for the 2 trials: TMZ (n = 43)/GFT (n = 16); median treatment duration: 1.6 /1.8 mo; Grade 3–4 toxicity: lymphopenia 5 patients (12%)/0, fatigue 8 patients (15%)/2 patients (13%), Survival data for TMZ/GFT arms: 3-month survival rate: 58.1% (95% CI 41.2–73) /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 1.5–1.8) /1.8 months (95% CI 1.1–3.9); median time to neuro. progr.: 8.0 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 MMS score, and subjective cognitive function, 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 function 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.

Trial partly supported by AstraZeneca (Switzerland), Essex Chemie (Switzerland) and Swiss Federal Government.

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

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BACKGROUND: Neoplastic meningitis (NM) is a devastating neurological 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 tumor and QL history, neurological symptoms/signs, radiological findings, CSF cytology, treatment options, and outcome were sent to 29 neurologic and 42 medical oncology Services of the Regionale Piemonte (Italy). Data were centrally reviewed in a University Hospital to confirm the diagnosis and the final analysis. RESULTS: From January 2000 to December 2008, we enrolled 68 patients with suspected NM. Diagnosis was confirmed in 59 patients (87%). Diagnosis was pathologically confirmed in 27 of 59 (46%) patients while was clínico-radiological in 32 of 59 (54%). There were 59 females and 20 males with a median age of 59 years (range 38–80). The site of primary tumor was: breast in 25 of 59 (42%), lung in 18 of 59 (31%), unknown in 5 of 59 (8%), gastrointestinal tract in 4 of 59 (7%), skin (melanoma) in 3 of 59 (5%), miscellaneous in 4 of 59 (7%) patients. The systemic disease at the time of diagnosis of NM was progressive in 55 of 59 (95%) and absent/under control in 4 of 59 (7%) patients. Brain metastases were concomitant in 26 of 53 (47%) patients. The median latency between first symptom and NM diagnosis was 4 weeks (range: 0–26 weeks). Treatment for NM consisted in intrathecal chemotherapy with liposomal doxorubicin (14 of 59 patients) or local RT or bulky disease; 12 of 59 patients, RT + intrathecal chemotherapy (2 of 59), surgical removal of spinal bulky disease (1 in 59), whereas 30 in 59 patients (51%) underwent supportive care only. Median survival was 6.8 weeks. In a multivariate analysis, the only parameter that influenced the prognosis was Karnofsky < 60 (P < .0042).

CONCLUSIONS: This is the first Community Hospital-based regional study and highlights that the prognosis is poor compared with specialized University Hospitals and that half of the patients are candidates only to aggressive therapy.

O.24. STEM CELL TRANSPLANTATION FOR CNS RECURRENCE 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 on transplantation patients have showed 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 49 patients, of systemic disease in 13, and of CNS+systemic disease in 14. All patients were Karnofsky ≥ 60 (P < .0042). CONCLUSIONS: This is the first Community Hospital-based regional study and highlights that the prognosis is poor compared with specialized University Hospitals and that half of the patients are candidates only to aggressive therapy.

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
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 major 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, reliance on current 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 for 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 recent results demonstrate that active Notch signaling is important for the maintenance and growth of GBM-derived BTICs. Thus, the Notch signaling pathway might be an appropriate target for GBM therapy targeting BTICs.

**AIM:** We investigated the functional role of Notch signaling in BTICs by examining the effect of Notch inhibition on tumorigenicity and stem cell-like properties. **RESULTS:** Primary neurosphere cultures were established from xenografts originally derived from human primary GBM. All cultures were examined in vitro for tumorigenic properties. RESULTS: Primary neurosphere cultures were established from xenografts originally derived from human primary GBM. All cultures were examined in vitro for tumorigenic properties. Established GBM neurosphere cultures treated with DAPT, furthermore, displayed reduced expression of the NSC marker Nestin and increased expression of markers of the NSC lineage, suggesting increased differentiation. When neurosphere cultures were induced to differentiate during DAPT treatment, they showed an altered differentiation pattern, in accordance with the established role of Notch during cell fate decisions. Finally, the Notch signaling pathway was demonstrated to play a role in the in vitro tumorigenic potential of the GBM neurosphere cultures, as displayed by inhibition of cell migration, in a modified Boyden chamber, upon Notch blockade.

**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 preferential to ionizing radiation and chemotherapy as a result of altered checkpoint and DNA repair pathways with conventional tumor cells. 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 biospecimens 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 reduced 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 vivo and partially sensitized the tumors to ionizing radiation in vitro. 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, 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 CD44 loss of function studies. Malignant gliomas were induced in mice by transfecting plasmids encoding SV40T antigen and NrasG12V into the lateral ventricle of wild-type (CD44+/+ ) and knockout (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 SV40T antigen 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 perversial 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 regress as measured by bioluminescence imaging. 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 abolish when CD44 expression is rescued exclusively in the tumor cells. These in vivo glioma cells require a hyaluronan-rich environment, to facilitate tumor initiation and progression. Our results demonstrate that loss of CD44 impedes the development of malignant gliomas. Furthermore, the spontaneous regression of CD44−/− tumors suggests that CD44 may be crucial to maintaining a niche supportive of tumor cell self-renewal and survival. Ongoing studies will look at CD44 modulation of multivular transporter activity and sensitivity to chemotherapeutic agents because of loss of function of CD44.
Abstracts

**O.29. THERAPEUTIC TARGETING OF THE NG2 PROTEOGLYCAN WITH MAB 9.2.27 AND ADOPTIVELY TRANSFERRED NK CELLS LYSES HUMAN GliOBLASTOMA MULTIFORME IN VIVO**

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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 the antitumor effect of this therapeutic approach. 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-B, and IFN-γ-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+, CD11b positive that penetrated deep into the tumor of the NK + mAb-treated animals. Flow cytometric analysis revealed less M2 phenotype macrophages in this group compared with the monotherapy controls. Animals treated with NK cells recruited only uniformly double positive ED1+, CD11b-positive cells that were less abundant and remained at the tumor brain boundary. MRI 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 amenable 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, EGF-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 of the receptor or the specific immunogenicity of the vIII approaches directed against the intercellular signaling pathway, the ligand-binding capacity of the receptor or the specific immunogenicity of the vIII.

**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: Twenty-five 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 1yr postoperatively. Furthermore, we determined the volume of cerebral edema on pre- and postoperative (3 months) MRI scans. The prescriptive dose was 25 Gy prescribed to the 70%–85% isodose line. All mAb- and mAb-treated groups. Moreover, double-labeling revealed the greatest numbers of M1-type macrophages that were ED1+, CD11b positive that penetrated deep into the tumor of the NK + mAb-treated animals. Flow cytometric analysis revealed less M2 phenotype macrophages in this group compared with the monotherapy controls. Animals treated with NK cells recruited only uniformly double positive ED1+, CD11b-positive cells that were less abundant and remained at the tumor brain boundary. MRI 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 amenable therapy for treatment-resistant GBMs.
controls. Two patients (9%) had a partial response. No patients had a worsen-
ing 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: ONSM, 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 pre-
liminary 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 85% 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 this retrospective study in 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 intra-
cranial meningioma between 1985 and 2003; 159 females (70%) and 63 males (30%) with an average age of 53 (±13.9) years 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 ques-
tionnaire 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 lifetable statistics to each individual patient for the individual duration of follow-up. RESULTS: The overall survival at 5yr, 10yr, 15yr, and 20 years was 95%, 81%, 63%, and 54%. 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 15yr 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 (15%) patients did not show any remission and 46 (22%) had more symptoms. CONCLUSION: Despite the benign histology of meningio-
mas, the long-term survival is severely challenged by the tumor and its com-
plications; 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 EPENDYOMA: 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 prognos-
sis 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 possi-
bility, 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 sur-
gelactic 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 com-
plete 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 ex-
ceptions. Eleven of 22 patients obtained CR, only one had a neurologic
worsening. We compared the outcome of the 38 patients CR after one surgi-
cal 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 mor-
bitity and results improved during time. 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 epidemiological and the clinical, radiological, pathological, and management profile of all pediatric meningio-

mas surgically treated during the last 35 years in the Netherlands. MATERIAL
AND METHODS: All pediatric patients (~18 yr of age) with the diagnosis
meningioma, treated at one of the neurosurgical centers in the Netherlands
during the last 35 years, were identified in the PALGA database, the nation-
wide 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 con-
firmation of the original histology, or the original histological diagnosis was
changed after revision. Thus, 69 patients (37 males) for whom the initial histology 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 convex-
y (22%). Etiology: 11 patients (16%) had neurofibromatosis type 2 and 4
patients received prior radiotherapy. Histology: 42 patients (61%) had a
WHO grade I, with meningotheliomatous meningioma as most common his-

cological subtype. Five patients (7%) had a WHO grade III tumor. Surgery:
macroscopic total resection was accomplished in 31 patients (42%) and sub-
total 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 (0.27–18.7). A total of 22 radiological confirmed recur-
rence were diagnosed in 13 patients (59%) during a period of 3.9 yr
(0.1–26.3). Eleven tumors reoccurred 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 menin-

ECONOMAN. 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 menin-

EOMAS 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 RADIOTHERAPY
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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 pediatric primary brain tumors (craniopharyngioma, cerebellar astrocy-
toma, choroid plexus papilloma, glioma, and glioneuronal tumor) were
O.37. CI-PERINOMS: CHEMOTHERAPY-INDUCED PERIPHERAL NEUROPATHY OUTCOMES STUDIES MEASURESTudy, on behalf of the CI-PERINOMS Group, Italy

Chemotherapy-induced peripheral neuropathy (CIPN) is a major, frequent, and potentially dose-limiting adverse event of a wide variety of chemotherapy 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 study is expected to be finished by 2012.

O.38. GLUT1/SLC2A1 IS CRUCIAL FOR DEVELOPMENT OF BRAIN MICROVASCULATURE 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 brain-blood 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 (AJ), which together maintain the blood-brain barrier. 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.

W. Grisold, D. Psimaras, A. Argyriou, H. Kalofonos, N. Konstantinou, P. E. Choufour, C. Vlachou, O.35. STUDY OF A HIGH-PRECISION RADIOTHERAPY TREATMENT AVENUES TOWARDS RECOVERING BBB DISRUPTION IN DEVASTATING BRAIN DISORDERS

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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 represent important clinical implications for the development of new therapeutic avenues toward recovering BBB disruption in devastating brain disorders.

O.39. TIMP-1 AND THE TIMP-1 INTERACTING CELL SURFACE PROTEIN CD63 IN CULTURED ASTROCYTOMA DERIVED SPUTHERAPIC EXPRESSIO AND CO-EXPRESSION WITH 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 glioblastoma was associated with a shorter overall patient survival. Recent studies have suggested that TIMP-1 can prevent chemo-induced apoptosis in culture and, in a study, human brain epithelial cells (MCF10A), it was demonstrated that the interaction of TIMP-1 and CD63 is necessary for 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 chemo-resistance. 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 severe neurotoxicity led to protrusion of chemotherapy for many patients with malignant and even low-grade infiltrative gliomas. In the absence of solid incidence data, we were interested in reviewing the published experience of t-MDS/t-AML in this patient population. METHODS: 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.
O.41. CHEMOTHERAPY-INDUCED POLYNEUROPATHY SCORE (CIPS): A NEW TOOL IN THE DIAGNOSIS OF CHEMOTHERAPY-INDUCED POLYNEUROPATHY (CIPN) A. Grisold1, W. Grisold2, C. Dittrich2,3, and S. Obersdorfer1 1LBI Neurooncology, Vienna, Austria; 2Department Oncology, Vienna, Austria; 3Department of Nuclear Medicine, Klinikum Grosshadern, Munich, Germany

INTRODUCTION: Chemotherapy-induced polyneuropathies (CIPN) are representing a therapy-limiting factor in the treatment of different oncological diseases. Reliable detection and diagnosis of CIPN is imperative 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, practicable 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 prospective consecutive 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 KFH-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 (88%) developed a CIPN and 9 (60%) study participants an acute oxaliplatin-induced neurotoxicity. The results showed a significant correlation of the TNS and the CIPS to all 3 scheduled dates of examination, as well as over time. Gender and age had no influence on the development of CIPN.

O.42. THE POTENTIAL ROLE OF VASCULAR ENDOTHELIAL GROWTH FACTOR IN RADIATION NECROSIS OF THE BRAIN, FROM THE PATHOLOGICAL CONSIDERATION OF HUMAN SURGICAL SPECIMEN S. Moriyama1, M. Furuse1, R. Hiramatsu2, N. Nonoguchi1, S. Kawabata1, T. Kuroiwa1, M. Fukumoto2, M. Fukumoto2, and K. Ono3 1Osaka Medical College, Takatsuki, Japan; 2Tohoku University, Sendai, Japan; 3Kyoto University Research Reactor Institute, Kunitomo, Japan

PURPOSE: With the advancement of high-dose radiation technologies 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 molecular genetic perspective. Let’s think about the strategy to treat RN depending on the pathological findings and from literature.

O.43. HOT SPOTS IN 18FET-PET DELINEATE MALIGNANT TUMOR PARTS WITHIN SUSPECTED WHO GRADE II GLIOMA M. Kunz1, N. Thon1, S. Eigenbrod2, C. Hartmann1, J. Geisler3, H. Kretzschmar2, A. van Deimling1, G. Pöppel1, J. Toni3, and F. Kretz1 1Department of Neurosurgery, Ludwig-Maximilians University, Klinikum Grosshadern, Munich, Germany; 2Institute for Neuropathology, Ludwig-Maximilians University, Klinikum Grosshadern, Munich, Germany; 3Department of Neuroradiology, Institute of Pathology, Karl-Rupprecht University, Heidelberg, Germany; 4Department of Nuclear Medicine, Ludwig-Maximilians University, Klinikum Grosshadern, Munich, Germany

OBJECTIVE: This prospective study correlates metabolic maps of intratumoral [F-18]fluorodeoxyglucose (FDG) uptake kinetics with detailed histopathology 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 18FET-PET-guided serial stereotactic biopsy procedures were found suitable for stepwise histopathological 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 isocitrate dehydrogenase (IDH)/2 mutations by immunohistochemistry analysis, respectively. RESULTS: A total of 373 biopsy samples from 55 consecutive patients were analyzed. In 24 patients, 18 patients had a grade II glioma diagnosed. Homogeneous metabolic kinetics was significantly linked to histopathological homogeneity in 40 patients. In 15 patients, a heterogeneous FET uptake kinetic was found throughout tumor volumes and a pronounced topographic pattern with grade II+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 tumors with heterogeneous histopathology were MGMT methylated and 9 tumors showed IDH1/2 mutations. Both histopathologic parameters were homogeneously distributed throughout each tumor irrespective of an anaplastic focus. CONCLUSION: Homogeneous or heterogeneous glioma histology can be precisely delineated by dynamic FET-PET evaluation; an same anaplastic focus can be reliably identified. This finding has implications for prognostic evaluation, biopsy planning, and individualized treatment strategies.

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 performed 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 modalities, H&E staining showed marked angiogenesis and reactive astrocytosis at the boundary between the apparent necrotic area and the normal brain. We described this border zone as the “peri-necrotic” area. The most prominent vascularatures in this area consisted of a thin endothelium, mimicking venules, which is identified as telangiectasis. 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 bevazucizumab and removal of necrotic tissue showed the rapid shrinkage of the pre-lesional edema. 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 early phase of RN, anticoagulants may be effective for maintaining microcirculation by preventing such small venules and arterioles from the thrombotic obstruction. However, in the later advanced phase of RN, medical treatment 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 immediate symptomatic improvements, because of the effect of reducing VEGF in this area.

NEURO-IMAGING II

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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 marks the 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 longitudinalis (SLF), inferior fronto occipitalis (IFO), inferior longitudinalis (ILF), uncinatus (UNC), premotor fibers] in a series of 305 patients with gliomas (mostly low grade) involving the language areas or pathways. DTI–FT information were loaded into the neuronavigational system and combined intraoperatively with those obtained with direct electrical stimulation applied at subcortical level, with bipolar 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, functional and involved 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 motor deficit. The identified tract 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 METABOLOMICS (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 analysis by data-processing software Alcice2 for metabolomeTM ver1.0 (JEOL DATUM) and ADOMEWORKS/ModellBuilder ver.3.1 (Figs. searched for the parameters which characterize malignancy in loading plot. RESULTS: Water soluble metabolites: Surgical specimens were distributed to almost 2 domains (grade 1 and grade 2/3 domains). Two anaplastic and 1 atypical meningiomas were distributed the same domain, and malignant-type meningiomas were distributed over extremely near location in the grade II/III domain. Lipid soluble metabolites: Malignant-type meningiomas were distributed near location in the grade III domain. However, grade II domain was isolated. CONCLUSION: This study suggests that NMR-based metabolomics are very useful for prediction of malignant-type meningiomas that were histologically benign.

O.46. INTRAOPERATIVE AND INTEROBSERVER AGREEMENT IN VOLUMETRIC ASSESSMENT OF GIOBLASTOMA MULTIFORME RESCTION
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OBJECTIVE: The aim of this study was to analyze intraoperative 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 minimally 2 weeks. Intraoperative resection and interobserver agreement for PreTV, PostTV, and residual tumor volume percentage (RTV) were expressed in intraclass correlation coefficients (ICC). RESULTS: Intraobserver agreement is high for PreTV (ICC = 0.999), PostTV (ICC = 0.73 – 0.94) and RTV (ICC = 0.89–0.94), 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 of this study suggest that using absolute RTV values to relate the extent of tumor resection with survival may be unreliable. More research is needed before this method can be used as a valid endpoint for clinical studies.
offer the opportunity for customized target definition for radiotherapy, (ii) allow to modify the therapeutic program also by the patient enrollment into experimental trials, and (iii) permit to monitor more precisely the response to the treatment. However, data on early progression in GBM are still lacking. Herein, the incidence and the methods to identify this phenomenon were investigated. MATERIALS AND METHODS: Thirty-seven patients with newly diagnosed GBM were retrospectively analyzed. Early post-operative magnetic resonance imaging (EMRI) was compared with 1-mo postoperative imaging to evaluate the extent of surgery and to identify possible new areas of contrast enhancement (CE). To classify these areas of CE as suggestive of tumor growth or surgical effect, 4 different magnetic resonance imaging (MRI) approaches were compared: (i) EMRI diffusion, (ii) T2-weighted imaging, (iii) 1-mo diffusion, and (iv) 1-mo perfusion. RESULTS: Based on EMRI, 67% of cases were classified as incompletely resected. Seventeen out of 37 (46%) patients showed an increased area of CE between surgery and chemo-radiation. By EMRI diffusion, in 3 of 17 patients this new CE corresponded to an induced diffusion and before indicative of postsurgical infarct; in the other 14 of 17 patients, they were indicative of tumor progression or a combination of progression and infarct. Comparing T2-weighted imaging EMRI vs 1-mo, 9 of 17 showed an increase of edema, suggestive of tumor progression. In the new areas of CE by 1-mo diffusion, 2 of 17 patients showed the coexistence of reduced diffusion. Finally, by 1-mo perfusion, 11 of 17 patients showed the coexistence of hyper-perfusion. Considering EMRI diffusion and 1-mo perfusion, they provided the most similar classification with an agreement in 11 of 17 patients. It is noteworthy that the extent of resection does not seem to influence the rate of tumor progression: 33% of the patients that performed gross total surgery vs 40% of those partially resected, experienced disease progression. CONCLUSIONS: Further findings suggest that early progression frequently occurs in GBM between surgery and the beginning of adjuvant treatment. EMRI diffusion, identifying post-surgical ischemic areas, and perfusion, detecting neo-angiogenesis, seemed to be the more reliable approaches.

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 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 a new histological diagnosis of primary cerebral glioma. All subjects had a structured psychiatric clinical interview to diagnose or exclude MDD. Data are presented in 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 > .05) between MDD and functional impairment (KPS ≤ 70), current steroid use (KPS ≤ 70), history of depression, major (KPS ≤ 70), current anxiety, and comorbid depression 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. Those 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 nonimproved KPS ≤ 70. They may also consider screening those with epilepsy, who are an easily identifiable group. The lack of association with any tumor-related variables suggests that in glioma, MDD could be more representative of a psychological reaction to loss than a "direct" tumor disruption of neuronal emotional networks. However, more research on this question would be required.

O.50. PSYCHOLOGICAL FACTORS OF THE RETARDATION OF NEURAL 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 tumors 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-somatic, 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 = 40; with head brain n = 40). The Luria’s method of complex neuropsychological diagnostics (for children), projective drawings, Children Apperceptive Test: questionnaire of Parental Attitude, Spielberger 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.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: highgrade 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 22 patients (55%) 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.53. HOW TO BEST MEET THE NEEDS OF PATIENTS WITH A GLOBLASTOMA 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 of 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 its 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. 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.54. EPILEPSY AT THE END OF LIFE IN MALIGNANT GLIOMAS
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Epilepsy is common in patients with brain tumors. Frequently, an epileptic focus is the presenting clinical sign, but late onset epilepsy 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 as 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 32 (35.1%) 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 5 cases, seizures occurred less than the last month of life. In 74 patients, seizures occurred at any time from the beginning of the disease until death with a comprehensive neuro-oncological home-care program. Epilepsy at the end of life was higher in patients presenting late onset epilepsy (25 of 33, 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 epilepsy (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 of 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.

Glioma

O.55. INF-β SENSITIZES GLOBLASTOMA 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...
have demonstrated that the restoration of wild-type p53 activity also sensitizes glioma cells to temozolomide. On the basis of prior reports that demonstrated a sensitization of glioma cells to temozolomide by interferon-β (INF-β), we aimed at characterizing the underlying mechanisms in more depth. We report that human glioma cells uniformly express mRNA for interferon receptors I and II whereas only interferon receptor II protein is consistently detected by flow cytometry at the cell surface. INF-β strongly sensitizes glioma cells to temozolomide-induced reproductive cell death. This sensitization is independent of p53 as glioma cells with an siRNA-mediated silencing of the p53 gene become more sensitive to temozolomide after prior exposure to INF-β, too. Further, MGMT-negative glioma cells and transfectants genetically engineered to overexpress MGMT can be sensitized to temozolomide by INF-β. This effect of INF-β is observed in acute cytotoxicity assays and in clonogenic survival assays. Most importantly, there is also a sensitization of stem-like glioma cells to temozolomide by INF-β. In summary, we find that the INF-β-mediated sensitization to temozolomide is neither mediated nor limited to MGMT-negative or -positive cell lines, suggesting that INF-β might be a powerful adjuvant to increase the benefit from temozolomide chemotherapy in glioblastoma.

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 PATHWAYS

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INTRODUCTION: Chromosomes 1p and 19q deletions and TP53 mutations represented the two main genetic alterations described in low-grade gliomas (LGGs). Interestingly, non-R132 IDH1 mutations and TP53 mutations are often 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 1p36 or 19q deletion was observed in 19. Intriguingly, no data are available on the intermediate group of LGGs harboring a “null” phenotype (no TP53 mutation and no 1p19q codelletion). Recently, mutations ofotate 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 homogenous 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 grade II or III LGG, available paraffin-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 IDH2 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 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 IDH2 segregate in a distinct molecular subtype of LGGs.
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, 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.60. 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-methylguanin-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 favorable 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 = 59), 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-nine patients progressed and 17 patients died. The relative frequencies were 27.0% (24 of 89) for TP53 mutations, 41.1% (37 of 90) for 1p/19q codeletions, 43.8% (39 of 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. Sobel IDH-1/2 mutations were confirmed to predict longer survival.

O.61. A COMPREHENSIVE STUDY OF THE ASSOCIATION BETWEEN THE EGFR AND ERBB2 GENES AND GLIOMA RISK

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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 major 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. METHODS: 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 Colour-Word-Test; Trail Making Test (TMT) A&B; Orientation and Clock drawing. Within 4 days after surgery, a neurologic 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 dissect the influence of cognitive domains (eg, memory, executive functions) on performance of this patient group.

O.62. COGNITIVE DEFICITS IN PATIENTS WITH GLIOMAS IN ELOQUENT AREAS BEFORE AND AFTER AWAKE SURGERY

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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, EGFR and VEGFR, on glioma and glioblastoma risk. METHODS: We analyzed 191 tag single nucleotide polymorphisms (SNPs) capturing all common genetic variation of EGFR, EGFR, ERBB2, LRG1, LRG1, VEGFR, and V2RG2 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/Genetics 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 = .039, odds ratio [OR] = 1.67 (95% confidence interval [CI]: 1.14, 2.45). The Bonferroni correction made all P-values nonsignificant. One SNP rs4947966 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 glioblastoma 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 reevaluate these findings and evaluate the functional significance.

O.63. 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 cura-
tive treatment options are available. From that moment on, only suppor-
tive 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 infor-
mation on QOL in the end-of-life phase is available. The objective of 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. Physicians and the patients’ partners were approached for 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 loss 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 rela-
tives, 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 rela-
tives 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. In 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 remaining patients were diagnosed with oligodendrogliomas (n = 9), anaplastic oligodendrogliomas (n = 2), or WHO grade III oligoastrocytomias (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 (FACT-Br), feelings of depression and anxiety (HAD), 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). Comparison with general population controls, matched for age, sex, and educational level, showed poorer mental functioning (P = 0.002), but poorer mental functioning (P = 0.002). Expectantly, partners’ feelings of caregiver mastery (P = 0.000) and feelings of anxiety and depression (P = 0.000) highly predicted their physical functioning (P = 0.002) and neurological functioning (P = 0.015), but not cognitive functioning (P = 0.342) of the patient, were predictive of mental functioning of the partners. Neither patient nor partner variables predicted the physical functioning of the partners. Our study demonstrates that partners 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. GIBLIOSTOMA IN ELDERLY PATIENTS: HEALTH-RELATED QUALITY OF LIFE (HRQOL) IN A RANDOMIZED TRIAL COMPARING 6-WEK VS 7W TREADYER THERAPY (RT) VS 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 patients. 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

Neurolymphomatosis is a rare clinical entity characterized by infiltration of peripheral nerves, nerve roots, plexus, or cranial nerves by malignant lymphocytes. The NLCG 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 years) and median proportion (60%) of patients were similar in Groups A and C. NL was presented as the first manifestation of malignancy in 26% and 29% of Groups A and B, respectively. The predominant malignant cell type was B-cell, whereas T-cell type occurred in 25%, 23%, and 3% of Groups A, B, and C, respectively. Our results showed that at least two-thirds of patients affected by peripheral nerves involvement may present with clinical symptoms on first examination, in the middle of radiotherapy, after 2 cycles of chemotherapy, and compared the plasma IgE levels before operation, 1 week after operation, and the outcomes of the patients. METHODS: We used enzyme-linked immunosorbance assay (ELISA) to determine the plasma IgE levels of 25 normal subjects and 232 glioma patients (85 grade II glioma patients, 40 grade III glioma patients, and 107 GBM patients). We also collected longitudinal plasma samples from 70 patients with GBM and compared the plasma IgE levels before operation, 1 week after operation, in the middle of radiotherapy, after 2 cycles of chemotherapy, and after recurrence. We determined the correlation between plasma IgE levels and the outcomes of the patients. RESULTS: Plasma IgE levels were significantly lower in glioma patients (P = 0.004), low-grade glioma patients have lower IgE levels than high-grade glioma patients (P = 0.029). Oligodendrogial tumors have higher IgE levels than astrocytic tumors and mixed tumors both in grade II (P = 0.014) and grade III (P < 0.001) glioma patients. In 24 patients with paired preoperative and 2 cycles chemotherapy plasma samples, IgE levels increased after successful removal of the tumor (increase > 100 mg/mL, P = 0.002), and the increase correlated with the patients’ survival (increase > 100 vs ≤ 100 mg/mL, 127.5 ± 62.3 weeks, P = 0.012, log-rank). Plasma IgE level increase of > 100 mg/mL has 80% specificity and 78% sensitivity to predict the patients’ long survival (> 18 months). CONCLUSIONS: Plasma IgE levels can 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
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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 as an attractive strategy against GBM. Recently, data 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 bevacizumab for 3 weeks. Before sacrifice, animals were analyzed by magnetic resonance imaging (MRI) on a 7T Pharmascan Bruker). MRI protocols included T1- and T2-weighted sequences to assess tumor morphology and edema, MR spectroscopy to assess key metabolite concentrations, diffusion-weighted imaging to assess cellularity, and dynamic contrast enhancement MRI to assess tumor perfusion, and vascular permeability. After sacrifice, tumors are processed for histology, immunohistochemistry, and molecular analysis.

PHYSIOLOGICAL EFFECTS OF BEVACIZUMAB: We found that bevacizumab reduced tumor 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 periphery of the tumor was significantly increased. Key angiogenesis-related genes were upregulated 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, and a 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
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In the Hu paraneoplastic syndrome, a T-cell–mediated immune response targeted against the intracellular protein HuD is thought to be the cause of the neurologic disease and neuronal destruction in patients with HuD expressing tumors. 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 and (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 (DCs), and DCs loaded with HuD protein, HuD peptide fragments mix (protein-spanning, overlapping 15-mers), PP65 protein, or PP65 peptide mix were added to the subsequent cultures. Readout by intracytoplasmatic IFN-γ staining and IFN-γ production upon stimulation with PP65 mix was not significant. In the second experiment, PBMCs were drawn from 4 patients with a definitive diagnosis of Hu–PNS and divided in to 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 PP65 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 positive results to HuD protein or peptides. One of the patients was CMV seropositive, and indeed showed IFN-γ production upon stimulation with PP65 mix. These experiments show that, although our methods were successful in the context of an infectious/inflammatory setting, they fail in the setting of HuD-specific T cells. The culture strategy does not stimulate HuD-specific T cells properly, or our readout methods are 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-cell lines would enable us to validate the methods used so far to detect HuD-specific T-cell, and would offer an unique opportunity to study HuD-specific T-cell function in vitro.

P.001*. PROTEIN TYROSINE PHOSPHATASES IN GLIOMA BIOLGY
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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
P.003*. METABOLIC CHARACTERIZATION OF STEM-LIKE GliOMA CELLS IMMOBILE AND CAN BE A TARGET FOR NOVEL GLIOMA THERAPY

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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 control by cDNA microarray analysis. Among the 4 genes identified, we focused on a membrane protein, urokinase-type plasminogen activator receptor 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 the members of urokinase plasminogen activator system since previous reports discussed its relationship to cancer metastasis in breast cancer. uPARAP 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 targeted uPARAP into different glioma cell lines (KNSM23 and KNSM21) 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 reorganization of the actin cytoskeleton. Downregulation of uPARAP could be a novel anti-invasion therapeutic strategy for malignant gliomas.
P.006. CARBON ION RADIATION WITH OR WITHOUT THE ADDITION OF CILENITIDE IS AN EFFECTIVE INHIBITOR OF INTEGRINE-MEDIATED TUMOR CELL MIGRATION

BACKGROUND: Multiple extracellular matrix proteins have been described to promote glioma cell motility accounting for infiltrative growth. Fibronectine (Fn) and vitronectine (Vn) have recently been targeted by cilenitide (CTG), a cyclic peptide known to inhibit αvβ3 and αvβ5 integrins that interact with Vn (αvβ3/β5), and Fn (αvβ1/β3/β5)/others). Implemented in most in vitro and in vivo treatment regimens, radiotherapy responses were thus also shown to alter CTG 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, glioma cells were irradiated with single photon doses of 1, 2, and 10 Gy using 6 MV photons at a linear acceleration. Particle radiotherapy was applied with an extended Bragg peak (E = (128 ± 7) MeV/u, 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 applied on the upper well. After 24 h of incubation, cells were stained and analyzed microscopically by an investigator blinded to experimental setup. Quantitative FACS analysis of integrin expression was performed with a BD FACScan using PC- and FITC-labeled antibodies directed against αvβ3 and αvβ5. Expression of CTG was not altered by CGT. In migration assays, CGT inhibited transmigration through Vn- but not 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- but not Fn-coated membranes. FACS analyses revealed an increased expression of αvβ5, and αvβ3 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 a risk of promoting glioma cell migration on Vn and Fn, whereas 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.

P.007. IGF/IGFBP SIGNALING IN MERLIN-DEFICIENT TUMORS

All schwannomas, 50%–60% of meningiomas, 29%–38% of epiphenome- mas, and all tumors as part of the inherited tumor syndrome Neurofibromatosis 2 (NF2) are caused by loss of merlin. Current therapies for merlin-deficient tumors especially in NF2 are insufficient, leaving patients with severe morbidity. There is a need for new therapies. We focused on Schwannomas as they are a hallmark of NF2 and serve as a model for merlin-deficient tumors. We aim to define therapeutic targets for schwannoma treatment. Using our in vitro model for human schwannoma, we showed the overexpression/activation of platelet-derived growth factor receptor α (PDGFRα) and ErbB2/3 in schwannoma and strongly activa- tion of extra-cellular signal-regulated kinase 1/2 (ERK1/2) and AKT and increased proliferation which we successfully inhibited by Sorafenib, AZD6244, and Lapatinib. Basal proliferation was partly dependent on PDGFRα. The radiation dependence on ERK1/2 and ErbB2. Increased adhesion of schwannoma was also PDGFR-β independent. These data suggest the involvement of additional factors. We have in this study investigated insulin-like-growth-factors-I/II (IGF-I/II) as they are important for Schwann cells, regulate adhesion, proliferation, and survival as well as ErbB1/2, AKT/FAK basically activated in schwannoma and are upregulated in cancers. IGF-binding proteins (IGFBPs) are also upregulated in cancer- regulating cell proliferation, differentiation, and survival. We show here that overexpression of IGFBP-1 are overexpressed in schwannoma cells and increase proliferation and adhesion. IGF-I receptor is also overexpressed and activated in schwannoma cells. We suggest that IGF/IGFBP system is involved in schwannoma development. Targeting IGF/IGFBP system together with PDGFR-β and possibly ErbB2/3 pathways would be an excellent approach in schwannoma treatment. We show dissocation of respective pathways that seem crucial for any educated drug therapy being mono or combinatorial therapy.

P.008. DOES BIPARTITE CLUSTER OF 7 + 46 MICRORNAS ON CHROMOSOME 14q32.31 PLAY A ROLE IN GLIOMAGENESIS?
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BACKGROUND: We demonstrated that gliomas exhibit a microRNA (miRNA) expression profile that is reminiscent of neural precursor cells (NPCs) (Lavon et al. Neuro-Oncology, 2010). There are obvious similarities in the self-renewal capacity of stem cells and cancer cells but the tumorogenic role of miRNAs that display similar expression profile in gliomas and nontrans- formed NPCs have not been established yet. The bipartite cluster of 7 + 46 miRNAs on chromosome 14q32.31 was uniformly downregulated in all gliomas tissues as well as in NPCs. This region is frequently deleted, or geneti- cally altered, in gliomas and in other haematopoietic and solid malignancies. Therefore, we assumed that it might represent a large tumor suppressor miRNA cluster. OBJECTIVE: To study the function of individual miRNAs from the miRNA cluster 14q32.31 in glioma migration, proliferation, and apoptosis. METHODS: We evaluated the role of the investigated miRNAs, we cloned the pri-microRNA into a lentivirus-based vector under the control of CMV promoter. This vector is co-expressing green fluorescent protein as a reporter gene, permitting tracking of infected cells. U87MG glioma cell line was transfected with either a lentivirus-based vector that contains one of the miRNAs on 14q32.31 or with an empty vector. Expression of the mature miRNAs was evaluated by real-time RT PCR. The effect of each miRNAs on cell proliferation was tested by cell titer blue assay. RESULTS: Enforced expression of individual miRNAs from the miRNA cluster on chromosome 14q32.31 was achieved by retroviral infection of U87MG glioma cell line. Overexpression of 14q32 miR1 reduced the proliferation rate of the U87MG cell line in a dose-dependent manner. Overexpression of 14q32 miR2 of the tested miRNAs (14q32miR1 and 14q32miR2) induced spheroid-like cell morphology. CONCLUSIONS: miRNA members derived from the miRNA cluster in chromosome 14q32.31 might play a role in the proliferation rate and morphology of gliomas. Further investigation is needed to uncover their role in gliomaogenesis. These miRNA on invasion, soft agar colony formation, and apoptosis is currently tested in vitro and their effect on tumorigenicity is investigated in vivo.

P.009. BIM MEDIATES GEFITINIB-INDUCED APOPTOSIS IN GLIOMA CELL LINES EXPRESSION OF ERBB2
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BACKGROUND: Tyrosine kinase inhibitors (TKIs), as gefitinib, are cur- rently used for the treatment of human tumors, including malignant glioma as a second-line treatment. Previous studies in lung cancer have observed that Bim, a pro-apoptotic protein from the Bcl2 family, is involved in the apoptotic effect of TKIs. They also propose that either inhibition in PI3K/Akt pathway or MEK/Erk pathway causes an increase in Bim levels. In this study, we analyze the apoptotic effects of gefitinib treatment and Bim expression in glioma cell lines. MATERIAL AND METHODS: Seven glioma cell lines (U118, SW1088, A172, SW1783, GOS3, SF767, and T98G) were treated for 48 hours with 10 μM of gefitinib or with solvent DMSO alone in a serum-free medium with 100 ng/mL of EGF. Apoptosis was assayed by flow cytometric analysis by Annexin V-FITC staining. Protein and expression of Bim and Akt, p-Akt, p-Erk, and tubuline were performed by Western blot (WB) using total protein isolates from cell cultures. For WB, before collecting, cells were treated for 15 minutes with 50 ng/mL of EGF to activate the EGFR pathway. Detection was performed with HRP-conjugated secondary antibodies and quantification of proteins bands was carried out with Odyssey (Licor Bioscience) software.

The data confirm the presence of Bim in both cell lines as well as in the other tested glioma cell lines. No significant differences were found in the expression of Bim after treatment with gefitinib. However, in the 5 cell lines that did not suffered apoptosis, 2 of them (GOS3 and SW1088) showed a reduction in p-Akt and an increase in Bim expression after gefitinib treatment. A decreased level of p-Erk in the other 3 cell lines.
P.010. ROLE OF KITENIN IN MIGRATION AND INVASION OF U251MG HUMAN MALIGNANT GLIOMA CELLS
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OBJECTIVE: Wnts have important roles in multiple cellular processes during development, including cell differentiation, migration, polarity, and proliferation. 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 transfecants (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 luciferase 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 luciferase 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/PCP signaling cascades and through downregulation of the c-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 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 transient 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 THBS-1 and consequently 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.

P.012. INCIDENCE OF LOSS OF HETEROZYGOSITY IN CHROMOSOMAL REGION 14q32.31 WHICH CONTAINS THE LARGE 7 + 46 BIPARTITE MICROSATNA CLUSTER, AND ITS RELATIONSHIP TO OTHER MOLECULAR MARKERS IN 95 GLIOMAS
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BACKGROUND: We demonstrated that the large 7 + 46 bipartite Dlk1-Dio3 microRNA cluster on chromosome 14q32.31 is uniformly downregulated in gliomas, embryonic stem cells, and neural progenitor cells. It might suggest that this cluster probably represents the largest tumor-suppressor microRNA cluster. Because the individual microRNAs from this large microRNA cluster are expressed only from the maternally inherited allele, deletion of the active allele may result in complete silencing of these microRNAs. There is strong evidence that this chromosomal region is frequently deleted or genetically altered in both haematopoietic and systemic solid tumors. In a preliminary small scale survey, we found a low rate of loss of heterozygosity (LOH) in this chromosomal region of only 5% in oligodendrogliomas and 35% in glioblastomas. The aim of this study was to verify the incidence of LOH in chromosome 14q32.31 and whether it might carry a potentially meaningful explanation for the previously observed downregulation of 7 + 46 bipartite microRNA cluster in gliomas. In addition, we examine whether there is any relationship 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 assay was performed on DNA that was extracted from paraffin-embedded samples of 95 gliomas. LOH of 14q32.31 is evaluated by using D14S65 at 14q32.2 and D14H22 at 14q32.31 markers. The analysis includes 39 oligodendrogliomas (54% WHO grade II) and 55 astrocytic tumors (46% WHO grade III and IV). The final data analysis and the correlation between 14q32.31 LOH and other markers will be presented at the conference.

P.013. RADIO-CHEMOTHERAPY RESISTANCE OF HUMAN GLIOMA: A ROLE FOR AKT INHIBITION
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Standard treatment of glioblastoma multiforme (GBM) consists of surgery, radiotherapy, and temozolomide (TMZ). Clinical data show that GBMs with wild-type methylguanine methyltransferase (MGMT) gene, which express the MGMT DNA repair protein, are resistant to TMZ. The PI3K/Akt “survival” pathway, which is activated in the majority of GBMs, is a main determinant of radioresistance. Activation of the pathway is mediated by the tumor suppressor gene PTEN and by EGFR. The prostate inhibitor nitramine (NFV) has been identified as downregulator of this pathway via inhibition of its key protein Akt. Our studies focus on the interaction between irradiation, TMZ, and NFV in human established and long-term primary glioma cell lines with known genetic profile with regard to PTEN, EGFR, and MGMT. Cell lines were tested on expression of the MGMT protein and on key proteins of the PI3K/Akt pathway. Cell survival was determined by clonogenic assay. A clear correlation was found between the sensitivity of glioma cells to TMZ, both with expression of the MGMT repair protein and with MGMT gene promoter methylation. Enhancement of the radiation response by TMZ was noticed in 3 of 5 MGMT promoter methylated, TMZ-sensitive cell lines. Treatment of D384 cells (methylated MGMT; wtPTEN) with NFV alone for 24 hours decreased cell proliferation and was cytotoxic at doses exceeding 30 μM. Pretreatment with 20 μM NFV for 24 hours enhanced the radiation response. The data indicate that targeted interference with disturbed molecular pathways in GBM is a promising approach to circumvent resistance to current therapies.

P.014. EGR-2–MEDIATED ACTIVATION OF BAK EXPRESSION IS INHIBITED BY THE NUCLEAR LOCALIZATION OF UPAR IN GLIOMA CELL LINES
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Glial 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 uPA/uPAR system has been postulated to play a central role in the mediation
of these processes. We have demonstrated previously that the simultaneous downregulation of uPAR and αvβ3 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 αvβ3 retarded mitochondrial Δψ collapse induced from Fas-PT enucleation 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.

**EPIDEMIOLOGY**

**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 tumors 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 was tabulated and a two-tailed χ² 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. Twenty 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 neurology at the time of referral and 70% of patients had a Glasgow coma score ≥ 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, LANGEUDOC 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, 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, neuropathologists, and neuromontologists, in collaboration with epidemiologists and biostatisticians, have established the French Brain Tumor Database (FBTDB, https://fbdtn.fr) 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 diagnosed WHO grade II glioma (g) in each case, collection of the personal 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 intraregional distribution of all cases in 6 French regions: Alsace, 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.
QUALITY OF LIFE

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 that “a “key worker” should be allocated to all patients with a diagnosis of intracranial tumor. It is a common practice that a neuro-oncology specialist nurse (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 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.019. NEOPLASTIC DIAGNOSIS TIMING PROFILE IN VON HIPPEL–LINDAU’S DISEASE: A PERSONAL SERIES EVALUATION

INTRODUCTION: Von Hippel–Lindau’s (VHL) disease is a rare autosomal-dominant genetic disease, with a prevalence close to 1 in 40,000 inhabitants. The affected patients present nervous system and retinal hemangioblastomas (HGBs) associated among others with paragangliomas/pheochromocytomas (PGLs), endolymphatic sac tumors (ELST), and renal cell carcinoma (RCC). The object of this study is to evaluate the presenting timing profile of these tumors in a series of affected patients. MATERIALS AND METHODS: Age and sequence of imaging confirmed diagnosis of intra- cranial arterial aneurysms, 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 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–confirmed carrier patients 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 (APLUSONS). 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 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 regularly following patients, in order to obtain an early diagnosis and adequate management of these neoplasms.
P.022* 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 BORTEZOMIB

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INTRODUCTION: Bortezomib-induced peripheral neuropathy (BIPN) in patients with multiple myeloma (MM) presents in up to one-third of multiple myeloma (MM) patients treated with bortezomib (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 BPN (J. Peripher. 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 reduction (TNSr), and compared. QLQ-CIPN20 was completed 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 were reported significantly more sensory (P = .01) and motor (P = .05) problems on the QLQ-C30 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 = .001) 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.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 allows a detailed 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 reported fatigue and sometimes altered mood. A comparison with the preoperative test showed poorer verbal fluency, attention, verbal or visual learning, or psychomotor speed. Cognitive function did not differ between the evaluation before surgery and follow-up and a high proportion of patients had a good recovery of cognitive functions and were able to carry out everyday activities.

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-spinal radiotherapy (54 Gy on the posterior fossa and 36 Gy on the nevraxis). 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 the present work was to compare the changes observed 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 were reported significantly more sensory (P = .01) and motor (P = .05) problems on the QLQ-C30 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 = .001) 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.025* CHARACTERISTICS OF SPONTANEOUS 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 control group for an interview setting before awake craniotomy. Three different topics were discussed with a minimal intervention of the interviewer; medical status, work, and hobbies. In the control group, most 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.
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 completion 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 of brain tumor patients pre- and postoperation. 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 role of the caregiver in the care 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 (CQOLC) was given to caregivers at baseline as part of a series of validated instruments to assess involvement and impact on them. The CQOLC 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 CQOLC has a maximum score of 140 points, with a higher score reflecting better QOL. RESULTS: Completed CQOLC questionnaires were collected from 22 caregivers to date. Of the 35 items, the 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 < 0.01) 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 < 0.05) and feel that their life is imposed upon (P < 0.02), while caregivers of patients with recurrent MG were significantly more satisfied with their sex lives (P = 0.03).
CONCLUSIONS: Results demonstrate the heavy burden placed on caregivers of patients with MG, particularly for those caring for newly diagnosed patients. This burden is greater than that reported by caregivers of patients with HGG, while this may be related to the neurologic compromise 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 MENINGIOMA 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) may more readily damages healthy brain tissue compared with meningioma (MG). Surgical resection may diminish the pressure imposed upon (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 COMPPLICATED WITH MALIGNANT BRAIN TUMORS: EFFICACY OF GOREISAN (AN AQUAPORIN INHIBITOR)
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OBJECTIVES: Glyceol, steroids, and isosorbide, which are covered by Japanese national 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 dampness, such as goreisan. Goreisan constitutes of 5 types of herbs-Polyergus 3 g, Rhizoma Alismatis 3 g, Pois 3 g, Ramulus Cinnamomi 1.5 g, and Rhizoma Atractylodis 3 g. It is well known as an aquaporin inhibitor to suppress pathologically emerged aquaporin 4 which increases in various pathological conditions such as malignant brain tumor, trauma, cerebrovascular disease, and so on. METHODS: Between October 2006 and February 2010, goreisan was prescribed to 63 cases (52 patients: males 29, females 23; ages range between 24 and 83 years, mean 55.4) with malignant brain tumors (primary tumor 16 patients and metastatic tumor 36 patients). Headaches were complained in 23 cases, and focal neurological deficits were complained in 44 cases. The efficacy was evaluated with improvement rate of symptoms and neurological deficits: excellent (improvement rate >50% or higher), good (improvement rate <50% or can significantly reduce the dose of glyceol and steroids), no effect, and deterioration. RESULTS: Excellent 18 (28.5%), good 30 (47.6%), and no effect 15 (23.8%). No significant complications were recognized. CONCLUSION: Goreisan can be used as a substitute for glyceol, isosorbide, and steroids to reduce mild brain edema.

P.029. STRENGTH OF SKELETAL MUSCLE IN GLOBLASTOMA 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 therapy 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 = 41 (patients 3), 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% to +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 2, value decreased by 3%). Extension of left knee decreased in all 4 patients (Patient 1–4: 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 to be useful in GNM 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.030. REHABILITATION OF PATIENTS WITH MOTOR DISORDERS AFTER SURGICAL TREATMENT OF LOW-GRADE GLIOMAS
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BACKGROUND: The increase of quality of life in patients with low-grade gliomas (LGGs). Motional defects are a basic factor that reduces quality of life of patients. AIM AND METHODS: We refer brain gliomas to infiltratively growing tumors, when zones of brain, which are functionality important for speech and motion and median structures, are involved in tumor process. After tumor removal, the motor defects can be appeared or increased in its severity. Image-guided surgery and laser thermodation allow to perform safe tumor resection within growth border. Thirty-seven patients LGG with motional defects in early postoperative period received recovery treatment. Treatment course includes pharmacotherapy (prozerin, vitamin preparations, physiotherapeutic methods (electro-miostimulation, lasertherapy), massage, medical gymnastic, and psychotherapy that depends on neurological disorders. The programs of individual recovery treatment depended on the volume of tumor resection, preoperative neurological disorders, and associated diseases. It allowed to improve the results of treatment of patients with LGG and promoted their social adaptation, provides high quality of life. RESULTS: All the patients had early renewal of the broken functions: multiplying the volume of active motions, improvement of walking and degree of domain domestic skills, positive psychotherapeutic effect. CONCLUSION: This study indicates that early differentiations complex rehabilitation treatment effectively corrects neurological abnormalities and provides high quality of live of patients with LGG.

IMMUNOLOGY AND IMMUNOTHERAPY

P.032. 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.
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 (CYP) depletes macrophages from the cancer site and enhances 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 tumor recurrence. 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 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 IL-1b signaling. Interestingly, IL-1b is an inflammatory cytokine with strong tumor promigratory properties and the antagonist for IL-1 receptor (IL-1RA) is being tested for cancer treatment. We have then observed that IL-1b 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 broader 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 synergetic 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 FEFD 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 CD8+ and CD4+ T-cell responses against 2 novel antigens, transferrin receptor and calgranulin B. 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 class.
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-regulated 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 both dexamethasone 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 is a potent chemoattractant 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.040†. SCREENING CHEMOTHERAPY AGENTS USING SURGICALLY OBTAINED BRAIN TUMOR SPECIMENS
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P.041*. STROMAL-DERIVED FACTOR 1A (SDF-1A), A HOMING FACTOR FOR MESENCHYMAL PROGENITOR CELLS, IS ELEVATED IN TUMOR TISSUE AND PLASMA OF GLIOMA PATIENTS
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P.038*. ESTABLISHMENT OF TEMOZOLOMIDE-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 in vitro and analyzed their molecular characteristics including MGMT status. RESULTS: To establish the TMZ-refractory glioma cell lines in vitro and analyzed their molecular characteristics including MGMT status. CONCLUSION: The newly established cell lines would be useful in the development of in vitro and in vivo TMZ-resistance experimental models.

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 brain-derived stem/progenitor cell lines like Nestin-positive fetal murine neural progenitors (NPCs), DCX-positive adult murine neuroblasts, and CD133+ human glioblastoma-derived cancer stem cells (CSCs), all cultured under serum-free conditions. Measurements are performed at Bruker Avance 600 MHz (14.4 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 the key link between the fundamentals of stem cell identity 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.
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 neural 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 ARC 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 by Spearman’s rank correlation. cASPM is an independent prognostic confounder 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 factor for a favorable patient outcome and is associated with a less 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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The methylation status of the MGMT \((O^\beta\text{-methylguanine-DNA methyltransferase})\) gene has been shown to be a predictive marker in high-grade gliomas treated with temozolomide. Methyltransferase-specific PCR (MSP) is widely used for the detection of the MGMT methylation. Despite its widespread use, MSP has several disadvantages. False positives can arise if primers are badly designed or used at too low a temperature. Moreover, MSP is a semiquantitative, but serial dilution methylation-specific melting analysis (HRM) can detect MGMT methylation with high sensitivity and estimate quantitatively the extent of methylation in tumors. We used genomic DNA derived from 72 high-grade gloma samples and unival methylated/unmethylated DNA standards. After boulfite treatment, PCR was carried out in the presence of dye to fluoresce when intercalated with double-stranded DNA. Methylated and unmethylated DNA acquires different sequences resulting in PCR products with markedly different melting profiles. By comparing the melting profiles of unknown samples with the profiles of methylated and unmethylated template ratio, we were able to estimate quantitatively the methylation levels of samples. It took us only about 90 minutes to get the data from PCR. MGMT methylation could be detected at levels as low as 1%. Methylation level measured by this assay was inversely correlated to the MGMT mRNA expression level quantified by real-time RT–PCR. High-grade gliomas with MGMT methylation <40% showed significantly short progression-free survival. Methyltransferase-sensitive HRM is the rapid and useful method for predicting the effect of Temozolomide in high-grade glioma therapy.

P.044. METHYLATION-SENSITIVE HIGH-RESOLUTION
MELTING ANALYSIS: QUANTITATIVE ASSESSMENT OF
MGMT PROMOTER METHYLATION IN HIGH-GRADE
GLIOMAS
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METHYLATION-SENSITIVE HRM is the rapid and useful method for predicting the effect of Temozolomide in high-grade glioma therapy.
wild-type patients to have a superior survival in the cetuximab-treated cohort but not in the sunstimib cohort. CONCLUSIONS: We confirm in this study, population that mutation of the IDH1-gene is correlated with the WHO 2016 glioma classification 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 isoforms 1 (IDH1) and 2 (IDH2) have been recently described in a high percentage of gliomas. Idiozytic and oligodendrogliomas. The two isoforms catalyze the conversion of isocitrate to a-ketoglutarate with reduction of NADP+. Mutations are preferentially located in exons 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 oligodendrogliomas), and 44 grade II–II gliomas (10 pilocytic astrocytomas, 10 diffuse astrocytomas, 24 oligodendrogliomas). 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 oligodendrogliomas grade II, 36% of oligodendrogliomas 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 = .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 tumor recurrence in glioma patients responding to chemotherapy. PATIENTS AND METHODS: Serial samples of 22 patients with recurrent glioma were measured and a Kaplan–Meier curve was drawn for high and low serum concentration S-100B. Our aim was to evaluate the value of S-100B in serum as a prognostic marker in tumor recurrence in glioma patients responding 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 GLIOBLASTOMA 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 O6-methylguanine DNA-methyltransferase (MGMT) promoter methylation status and Ki-67–labeling index, and response to temozolomide (TTM), 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–ِ] August 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. Methyltransferase-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 excluded because of tissue sample loss, and 31 patients were included in this study. Population that mutation of the IDH1-gene is correlated with OS may be present in patients treated with the anti-EGFR–targeted mAb cetuximab. Further study is currently ongoing in one-third cohort but not in the sunstimib cohort. 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 = .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.

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 fraction (IPF) may serve as predictor of TMZ-induced thrombocytopenia in malignant glioma patients. The IPF has been suggested to reflect platelet turnover and has been proposed as useful marker for monitoring chemotherapy. CONCLUSION: The 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.

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 tumor recurrence in glioma patients responding 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 pg/ml). 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 = .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.
The highest combination of sensitivity and specificity was observed for an IPF change of 0.014 percentage-points per day. At this cutpoint, the sensitivity, specificity, PPV, and NPV for prediction of significant thrombocytopenia were 60%, 67%, 7%, and 97%, respectively. CONCLUSIONS: Low sensitivity, specificity, PPV, and NPV indicate that the time course of PLT counts and IPF measured at routine clinical follow-up are not useful for prediction of thrombocytopenia 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 target for cytotoxic NADPH overproduction 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 83 gliomas 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), 3 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), 7 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). 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) OA; 100% (3/3) PA; 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 7 (23%) tumor samples. Patients with mutated IDH1 showed an increase in overall survival (median survival 38.9 vs 5.4 months in non-mutated cases; P = 0.007). Genetic alterations in TP53 were found in 4 (50%) tumors with mutated IDH1 and 3 (13.6%) gliomas without IDH1 mutation. Median survival of patients harboring mutations in both genes was 48 months, while median survival of those with mutation in one of the genes and unmethylated MGMT promoter 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 prognostic 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 identified 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.

Brain tumors occur in all age groups and represent the leading cause of cancer-related death in children and young adults. The overall survival of patients with brain tumors is poor, and the long-term survival rate is less than 30%. The prognostic factors that influence the response to therapy and survival include intrinsic tumor properties, age, and extent of surgery. In this study, we aimed to investigate the relationship between the expression of Runx3 and the methylation status of its promoter region.

In this study, we analyzed the methylation status of the RUNX3 promoter region in a series of 18 recurrent gliomas. We used bisulfite genomic sequencing (BGS) to analyze the methylation status of the RUNX3 promoter region. We found that the methylation status of the RUNX3 promoter region negatively correlated with the expression of the RUNX3 gene.

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 cytosolic isocitrate dehydrogenase I, were reported to occur at high frequency in gliomas and association with overall survival was found. Genetic alterations 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 glioblastoma multiforme gliomas and 20 supratentorial gliomas were included. 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 (27%) glioblastoma multiforme gliomas and 2 (10%) supratentorial gliomas. All genetic alterations were identified in 5 glioblastoma multiforme gliomas and 1 supratentorial glioma. Patients with IDH1 mutations were younger (median age 35.5 vs 54 in non-mutated cases; P = 0.001) and had better overall survival (median survival 32.1 vs 5 months in non-mutated cases; P = 0.01). Mutations in TP53 were detected in 7 (23%) tumor samples. Patients with mutated TP53 showed increase in overall survival (median survival 38.9 vs 5.4 months in non-mutated cases; P = 0.007). Genetic alterations in TP53 were found in 4 (50%) tumors with mutated IDH1 and 3 (13.6%) gliomas without IDH1 mutation. Median survival of patients harboring mutations in both genes was 48 months, while median survival of those with mutation in one of the genes and unmethylated MGMT promoter 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 prognostic biomarkers in Bulgarian patients with gliomas.

P.053. BEVACIZUMAB-BASED THERAPY RECURRENT 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). The 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 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 progressions (42%) were observed. Eight patients showed an improvement in neurological signs and symptoms. Rasm’s sVEGF 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 sVEGF and pVEGF levels at baseline compared with the younger ones (<40 years). CONCLUSIONS: BV-based therapy showed activity in patients with heavily pretreated recurrent MGGs. 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 S. Haapa-Paananen1, 2 S. Kiviluoto1, M. Waltari2, M. Puputti2, J. P. Mpindi1, 3, P. Kohonen1, O. Tynninen4, H. Haapasalo5, H. Joensuu2, M. Peralta1, and O. Kallioniemi1, 3, 1Medical Biotechnology, VTT Technical Research Centre of Finland, and Centre for Biotechnology, University of Turku, Turku, Finland; 2Department of Oncology, University of Helsinki and Helsinki University Central Hospital, Helsinki, Finland; 3FIMM – Institute for Molecular Medicine Finland, University of Helsinki, Helsinki, Finland; 4Department of Pathology, Helsinki University Central Hospital and University of Helsinki, Helsinki, Finland; 5Department of Pathology, Tampere University Hospital, Tampere, Finland

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 Affymetrix samples from the Genesapiens database (www.genesapiens.org) in order to identify the most glioma-specific biomarkers. We searched for genes that were highly expressed in 322 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. Transcription 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 characterized its expression by immunostaining and functional role by silencing HES6 using 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 normal brain tissue controls. Positive HES6 immunoreactivity was present in 99% of available gliomas. Recurrent tumors of grade 2 astrocytomas and grade 2–3 oligodenrogliomas 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.055*. GSHP-Congjugation Improves Efficacy of Doxil Against Intracranial XenoGrafts

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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 anti-oxidant that is found at high levels in the brain and its active transporter is abundantly expressed at the BBB. Previous studies using microdialysis with an increasing % of GSH conjugated to liposomes carrying ribavirin have shown a GSH-dependent increase of drug levels in brain interstitial fluid (up to 3-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 Dx-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 Dx-equivalents. Moreover, 5% GSH-Doxil and 3% 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 and precluded further testing. In this series, the variably positive tumor response was small. There was again 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 groups. This growth delay was a significantly increased median survival of 32.5 days relative to 27 days for untreated controls. The response in the 3% 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? D. Nesbitt, G. Hendry, D. Scoones, and P. Kane; Department of Neurosurgery, The James Cook University Hospital, Middlesbrough, UK

INTRODUCTION: Glioblastoma multiforme (GBM) is the most common and aggressive malignant primary brain tumor (MPBT). It is 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. METHODS: Retrospective analysis of follow up imaging and 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 month 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 modality, frequency, indication, and detection of symptomatic/asymptomatic tumor recurrence. 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 scans were performed on 100 patients, 54% of which were within the 12 + 2 week target. Thirty-two percent of scans were performed earlier than the 12 + 2 week target. 36% were undertaken because of a clinical deterioration in the patient, the main reason for the reduced time interval between scans. Of 124 scans that were detected, only 11 were asymptomatic. CONCLUSIONS: Guidelines relating to the follow up imaging of MPBT are limited. 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 that 3-month 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 MPBT treatment, as does the Cancer Council Australia. There is little of consensus and evidence regarding the post treatment imaging in patients with MPBT. Further studies are required to evaluate clinical and cost effectiveness.
P.057*. PERI-ICRTAL PSEUDO-PROGRESSION IN BRAIN TUMOR PATIENTS 
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BACKGROUND: During the follow-up of brain tumor patients, the appearance of new contrast-enhancing lesions on MRI frequently mimics tumor 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’s 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 ± 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 ± 2.3 years (range 1–7) since the initial peri-ictal pseudo-progression episode, two 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-irradiation cortical vasculopathy, with SNHL. Hypointensity of the affected labyrinth will result in a significant faster detoriation of PTA. Audiological detoriation 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 MRI 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
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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 radiation therapy and to optimize timing of radiological follow-up during treatment.

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 predicting outcome in glioma patients. It is adequate to restrict one to 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.058*. CORRELATION OF VESTIBULAR SCHWANNOMA VOLUME WITH GROWTH AND AUDITORY FUNCTION IN A W&S POLICY
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INTRODUCTION: A wait and scan policy (W&Ss) is often proposed in vestibular schwannomas (VS). In this policy, volume measurements have proven to be more reliable than two-dimensional measurements to establish tumor growth. In this study, we use a novel volumetric measuring tool to evaluate the correlation between VS volume and audiological function at diagnosis and during follow-up. In addition, risk factors (patient characteristics and symptoms, VS growth and morphology on magnetic resonance imaging (MRI)) predicting hearing loss and VS growth were assessed.

MATERIALS AND METHODS: MRI scans, corresponding audiograms (with results of pure tone audiogram (PTA) and speech discrimination score (SDS)) of 63 patients, were analyzed retrospectively. Of 56 patients, 2 or more MRI/audiogram combinations were available. Mean follow up was 21.6 months. Volume measurements were performed on contrast enhanced T1-weighted images (TE T1-W). Morphology was evaluated by checking the presence of central nonenhancement, VS stage and side and signal intensity of the affected labyrinth. Clinical charts were analyzed for symptoms. RESULTS: Growth occurred irrespective of hearing status (PTA/SDS), patient age, gender, VS side, symptoms at presentation and morphology (VS stage, nonenhancement, labyrinthine signal intensity), although significant growth in the first year was predicting further growth during FU. Patients complaining of sensorineural hearing loss (SNHL) showed significant worse hearing on PTA and SDS and a trend towards more profound hearing deterioration over time was seen. Hypointensity of the affected labyrinth was a strong factor of significant hearing loss over time compared with isointense labyrinths. Volume measurements did not correlate with audiological function and deterioration. CONCLUSION: Hearing loss was more profound, and hearing will deteriorate faster in patients presenting

P.060*. ANALYZING RESPONSE OF MALIGNANT GLIOMA TO BEVACIZUMAB USING HIGH-RESOLUTION MAGNETIC RESONANCE IMAGING AT 7 TESLA
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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 tumor 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 x 320; resolution = 0.75 x 0.72 x 0.7 mm; slices = 208; parallel imaging factor = 2, TR/TE/TI = 3800/1700/3.55 ms, acquisition time = 102.24 minutes. Contrast agent was injected in the 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

Abstracts
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 bevacizumab therapy (“primary bevacizumab resistance”). Advanced imaging modalities may improve assessment of response to bevacizumab therapy.

P.061* VALUE OF THALLIUM SPECT (SPECT) TO EVALUATE RESPONSE TO BEVACIZUMAB TREATMENT IN HIGH-GRADE GLIOMA 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, before and after treatment, in order to evaluate response correlation. PATIENT CHARACTERISTICS: Twelve out of 17 patients could be evaluated with both techniques: 11 in 16 patients. In the 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 16.7%, CR 8.3%. Response rate by SPECT was as follows: P 16.7%, SD 41.7%, PR 16.7%, CR 25%. Response by modified MacDonald criteria: P: 58.3%, SD: 8.3%, PR: 16.7%, CR: 8.3%. Coincidence between SPECT and 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 normalization of a previous positive SPECT lasting for 103 weeks while

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: NV 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 neurophysiological 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 INFAMMATION 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 effects of OVs is limited by a number of factors that 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 shows increased MPO activity after OV delivery. This enzymatic activity is reduced when animals are pretreated with cyclophosphamide. The MRI data correlate with immunohistochemical staining of phagocytic cells and ex vivo measured MPO mRNA levels and activity. We also show that this technique presents a unique spatial resolution wherein the inflammation process at the border and in the center of the tumor can be distinguished and provides us with information on tumor, size, and shape. The second technique allows 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 armed with a CEST-reporter gene to be tested in brain tumor oncolytic 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.

P.064. EVALUATION OF MODIFIED METHIONINE PET IMAGING TO DISTINGUISH RADIATION NECROSIS FROM RECURRENT MALIGNANT GLIOMA: THE NEW METHOD TO EVALUATE TISSUE PROLIFERATION

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13C-Methionine (MET) is useful for evaluating radiation necrosis (RN) and glioma recurrence. However, it is sometimes difficult to distinguish these lesions because the accumulation of MET is affected not only by tissue proliferative activity but also by vascular factors, such as the vascular bed volume or the disruption of BBB. RN has mild accumulation of MET mainly affected by the vascular factors. To exclude the vascular factors, we made modified MET (mod-MET) PET images. On the basis of our studies of infarction, accumulation of 13C-Choline (CHO) is thought to be mostly affected by the vascular factors. The vascular MET-SUV, which reflected only the vascular factors, could be obtained from the CHO-SUV using linear regression for MET-SUV and CHO-SUV of the choroid plexuses. The mod-MET PET, which is obtained by eliminating the vascular MET-SUV from the total MET-SUV, is thought to mostly reflect tissue proliferation. The differentiation between RN and recurrent glioma was studied by using MET, CHO, 19F-Fluorodeoxyglucose (FDG), and mod-MET PET. The PET images were obtained from histologically verified 16 RNs, 16 recurrent grade-3 gliomas (Gr.3) and 17 recurrent glioblastomas (Gr.4). All lesion/normal (L/N) ratios for Gr.4 were significantly higher than those for RN (P < .005), but there was significant difference between Gr.3 and RN only in the MET and mod-MET L/N ratios (P < .05). ROC analysis indicated that mod-MET PET was the most accurate for differentiating between RN and tumor recurrence. The best cutoff value of mod-MET L/N was 4.75, providing a sensitivity of 78.8% and a specificity of 93.7%. Even for cases in which RN is barely distinguishable from recurrent glioma according to the original MET-PET, the mod-MET-PET made it easier to visually distinguish these lesions.
P.065. FUNCTIONAL DIFFUSION MAP: NEW IMAGING ASSESSMENT OF GLOBLASTOMA PATIENTS TREATED BY BORON NEUTRON CAPTURE THERAPY

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INTRODUCTION: Assessment of therapeutic efficiency for glioblastoma (GB) patients is traditionally accomplished by measuring changes in tumor size on gadolinium-enhanced T1-weighted images at 3 months. 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 was 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) using this fDM analysis. MATERIALS AND METHODS: During 2003–2007, 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-Response Traj.1.0 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 and 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.

P.066. A RARE CASE OF EXTRA-AXIAL MEDULLOBLASTOMA PRESENTING WITH MULTIPLE CRANIAL NERVE THICKENING

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CASE REPORT: A 26-year-old male presented with left-sided hearing loss. MRI showed a small, subtle enhancing lesion in the left internal auditory canal (IAC), suggesting schwannoma. Steroid therapy was started, and the patient was referred and scheduled for surgery in our centre. Two months later, while on the waiting list, the patient noticed right-sided hearing loss. Repeated MRI demonstrated a new right-sided IAC lesion and increased left-sided IAC mass and subtile, bilateral thickening of cranial nerves III–X. Lack of enhancement was attributed to steroid effect. Within the next week, the patient developed progressive cranial nerve deficits. Neither extensive blood, repeated CSF examination, nor PET-CT directed towards inflammation or primary malignancy. Biopsy of the IAC-mass was proposed, but declined by the patient. Steroid therapy was continued with vasculitis as working diagnosis and symptoms improved. Twelve months after his first presentation, the patient presented with parentec foot muscleatrophy. Spinal MRI demonstrated small intradural, extramedullary lesions on C3 and Th11 and thickening of the cauda equina. In a multidisciplinary session, biopsy of the Th11-lesion was decided. However a few days later, patient deteriorated very quickly, and MRI showed posterior fossa masses and extensive supratentorial and infratentorial leptomeningeal deposits. The right frontal leptomeningeal lesion was biopsied. Microscopy showed small round blue cells, rosettes, and leptomeningeal proliferation. CD56 immunohistochemical staining confirmed neurogenic origin, Final diagnosis was desmoplastic/nodular medulloblastoma with leptomeningeal deposits. DISCUSSION: Medulloblastoma is the most common pediatric central nervous system malignancy, usually presenting as an intra-axial infratentorial mass. Adult cases are extremely rare (annual incidence 1 per 2–20 million). Leptomeningeal spread occurs in 33% of cases. Extra-axial presentation of medulloblastoma is extremely rare, with only 9 reported cases in literature, the majority presenting as cerebellopontine angle masses.

To our knowledge, medulloblastoma presenting as multiple cranial nerve involvement has not been described before.

P.067. UNUSUAL IMAGING FINDINGS IN A TEMPORAL LOBE HIGH-GRADE GLIOMA WITH INVOLVEMENT OF BRAINSTEM WHITE MATTER TRACTS

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INTRODUCTION: We present a multilinear brainstem lesion, in conjunction with a right temporal mass, which turned out to be an astrocitoma. 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 pleocyto-sis 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 high-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 hyperintense 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 GLOMUS

P.068. CONTRAST ENHANCEMENT ON INTRAOPERATIVE MRI: IS IT TUMOR?

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We describe a case of a patient with a right frontal glioblastoma. The tumor consisted of a large lesion and a ventral satellite lesion. Contrast enhancement of both lesions did not overlap. Both lesions were resected using ultra low-field strength intraoperative MRI (0.15 Tesla). The relation between contrast enhancement on intraoperative MRI and histological findings has not yet been evaluated systematically. This case report discusses intraoperative and histological findings, emphasizing several pitfalls involved in contrast dose and timing of contrast administration.

P.069*. PROGNOSTIC IMPACT OF STEM CELL MARKER CD133 IN GLOBLASTOMA PATIENTS TREATED WITH CONCOMITANT RADIOCHEMOTHERAPY: 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 tumorogenic 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 others (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 RECURRENCE AND PSEUDO-PROGRESSION IN GLIOBLASTOMA PATIENTS TREATED WITH POSTOPERATIVE RADIOTHERAPY WITH CONCURRENT TEMOZOLOMIDE


BACKGROUND: Combined postoperative therapy with temozolomide (TMZ) has become the standard of care for primary malignant 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 \( \geq 25\% \) 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, the patients were categorized as deceased or alive. RESULTS: A total of 136 patients were analyzed, 80 males and 56 females, median age 62 years (17–81), median Karnofsky performance index at diagnosis 70 (20–90). In total, 123 cases were primary GBMs, 13 were secondary, 13 patients had multifocal disease, 69 patients underwent macroscopically complete resection, 40 partial resection, 24 biopsy, 3 had no primary surgery, but were diagnosed by biopsy later. Seventy-three patients were intent to treat with concurrent chemo-radiation followed by 6 cycles adjuvant TMZ, of which 37 completed the full treatment as planned (50%). Median OS in the combined group was 16 months compared with 8 months in the other group \( (P = .00003) \). Pseudo-progression was observed in 10 cases in the combined group (16%) vs none in the other group using the strict criteria \( (P = .003) \). Applying more liberal criteria, pseudo-progression was found in 17 cases (27%) in the combined group vs one in the other group \( (P = .0003) \). The median time to pseudo-progression was 4 weeks after radiation. Only pseudo-progression assessed in tumor size or the occurrence of a new contrast-enhancing lesion, thus precluding the accurate assessment of any reduction in the tumor burden. The issue of a robust primary endpoint for phase II studies is therefore still open. The aim of the study was to evaluate outcome endpoints for second-line treatment at recurrence. METHODS: A retrospective analysis was made using a database on 653 GBM patients followed prospectively between May 2006 and December 2008. A total of 150 patients (median age: 52 years, \( 4–86 \)) 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, mPFS was 2.5 months \( (95\% \) CI: 2.0–3.1), mOS 6.5 months \( (95\% \) CI: 5.9–7.1), mPFS 6 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 patients, confirm the need to establish the cut-off for active cytotoxic drugs in phase II studies on recurrent GBM. For antiangiogenic compounds, OS can be considered as a sound endpoint.

P.071*. CAN OS-6 REPLACE PFS-6 AS A PRIMARY ENDPOINT IN PHASE II STUDIES ON GLIOBLASTOMA PATIENTS GIVEN ANTIANGIOGENETIC DRUGS?

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BACKGROUND: In the last decade, progression-free survival at 6 months (mPFS) has been considered the best endpoint in phase II trials on recurrent glioblastoma (GBM). However, since a “new standard” of care was established by the EORTC/NCIC phase III trial, no data have reported on the mPFS or overall survival (mOS) obtained with second-line treatment following combined RT/TMZ. Moreover, antiangiogenic agents might alter data on response by repairing the blood–brain barrier and diminishing contrast enhancement, thus precluding the accurate assessment of any reduction in the tumor burden. The issue of a robust primary endpoint for phase II studies is therefore still open. The aim of the study was to evaluate outcome endpoints for second-line treatment at recurrence. METHODS: A retrospective analysis was made using a database on 653 GBM patients followed prospectively between May 2006 and December 2008. A total of 150 patients (median age: 52 years, \( 4–86 \)) 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, mPFS was 2.5 months \( (95\% \) CI: 2.0–3.1), mOS 6.5 months \( (95\% \) CI: 5.9–7.1), mPFS 6 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 patients, confirm the need to establish the cut-off for active cytotoxic 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 SIX-COURSE RADIOTHERAPY WITH CONCOMITANT AND ADJUVANT TEMOZOLOMIDE IN ELDERLY PATIENTS WITH GLIOBLASTOMA MULTIFORME

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INTRODUCTION: The EORTC (26981-22981)/NCIC CEG (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 19–71 (median 56 years), and this reduced benefit analysis for patients with an increase in age. A recent RCT in elderly GBM patients found improved survival with RT compared with supportive care alone and another study detected an increase in OS of 40 Gy/15 vs a 60 Gy/30 RT regime. 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 (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. Assuming accrual of 150 patients per year, 360 patients will be accrued in 3.7 years with final analysis after 5 years. Radiation and temozolomide were planned for a study duration of 5 years. Study Progress: The trial is open in Canada (NCIC CEG, Europe (EORTC), Australia and New Zealand (TROG), and Japan. As of March 1 2010, 123 patients were randomized. Median
age is 73 (65–86) years with 78% over the age of 70. Seventy-five percent of patients are ECOG PS 0 or 1 and 25% are ECOG PS 2; 69% had sub- or gross-total resection, 31% biopsy only. Discussion: The NCIC CTG CE.6 randomized trial alone vs RT and Adjuvant TMZ is an international cooperative effort addressing an important unmet need in the spectrum of care for newly diagnosed GBM.

P.073*. INFLUENCE OF HYPOXIA ON GLIOMA AND GLIOMA STEM-LIKE CELLS M. Sanzey 1, A. Gedebiewska 1, L. Vallar 1, and S. Niclou 1; 1Luxembourg Neuro-Oncology Laboratory, Centre de Recherche Public Santeé (CRP-Santeé), Luxembourg, Luxembourg; 2Microarray Center, Centre de Recherche Public Santeé (CRP-Santeé), Luxembourg, Luxembourg

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 cell-like survival 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 U87/3) 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 glial 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 transcriptional analysis based on cell survival data and protein expression profile of hypoxia inducible factor (HIF-1α). The cellular response to hypoxia was studied at the transcriptional 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 GLIOMA PATIENTS RESPONDING TO BEVACIZUMAB M. Eoli 1, A. Callieri 2, L. Cuppini 1, E. Mancuso 3, E. Prodi 1, S. Pellegatta 1, P. Porrati 1, M. Bruzzone 1, F. Bertolini 3, and G. Finocchiaro 1; 1Fondazione IRCCS Istituto Neurologico Carlo Besta, Milano, Italy; 2Istituto Europeo di Oncologia, Milano, Italy; 3Istituto Europeo Di Oncologia, Milano, Italy

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/mq 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 Karnovsky 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+ CD133+ /PhIh+2+ cells, whereas CEPs as CD45+/CD45- CD31+ /CD133+ + cells. CEC subpopulations were also enumerated. No severe side-effects were 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 = .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 (116 ± 52 vs 70.9 ± 55.3, P = .05 for CECs and 33.4 ± 18.3 vs 16.2 ± 16.4, P = .03 for CECs viable). No significant difference in CEPs number and viability among patients and during treatment was detected. The data suggest that investigation of CECs and/or CEPs during treatment 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 T. Fael Al-Maybani, E. Kettner, R. Ichimura, P. Collins, and C. Watts; University of Cambridge, Cambridge, UK

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 disease of the molecular signature of GBM-NG2+ and GBM-NG2– cells. METHODS: Methodologies comprised of a panel of immunohistochemistry techniques on clinical samples according to our Cambridge Protocol. GBM-NG2+ cells were sorted using FACS. Comparative molecular studies were conducted using microarray, comparative genomic hybridization (CGH), and Western blot. RESULTS: Microarray data indicated that NG2+ cells overexpressed a group of genes previously recognized by Cancer Genome Atlas within the Mitosis and Cell-Cycle Module (CCM). Array data analysis showed overexpression of unique set of proliferative pathways and transcription factors (TFs) by GBM-NG2+ cells. 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 tumorigenesis 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 MAPK/MAPK pathways.

P.076*. NEOADJUVANT TEMOZOLOMIDE FOR GRADE III AND IV ATROCYTOMA: A RANDOMIZED PHASE II STUDY A. Malmström 1, H. Skovgaard Poulsen 2, G. Stratiotii 3, B. Groberg 4, S. Hansen 5, T. Askland 6, and R. Henriksson 7; 1Unit for advanced palliative home care, University Hospital, Linköping, Sweden; 2Department of Radiation Biology, The Forsknings center, Copenhagen, Denmark; 3Department of Neurology, Karolinska University Hospital, Stockholm, Sweden; 4Department of Oncology, St. Olavs Hospital, Trondheim, Norway; 5Department of Oncology, Odense University hospital, Odense, Denmark; 6Department of Radiation Sciences, Oncology, Umeå University, Umeå, Sweden; 7Department of Oncology, Karolinska University Hospital, Stockholm, Sweden

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, concomitant radio-chemotherapy became standard treatment and was therefore incorporated in the later part of the trial. MATERIAL AND METHODS: Newly diagnosed patients with astrocytoma grade IV (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 91.3% 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.078. SMALL MOLECULE KINASE INHIBITORS IN GliOblAstoma: A SYSTEMATIC REVIEW OF CLINICAL STUDIES
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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 phase I trials. 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, PKCδ, and PDGFR).

P.079. NPAS3 IS A NOVEL LATE-STAGE ACTING PROGRESSION FACTOR IN GliOMA WITH TUMOR SUPPRESSIVE FUNCTIONS
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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 deleterions 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 a glioblastoma 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-genesis genes can transform a well-characterized TERT immortalized human astrocyte cell line and promote the growth of anaplastic astrocytomas. CONCLUSION: Our data provide compelling support of NPAS3 as 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
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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 modified serum-free media that promotes the growth of stem cells over a period of 10 days 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
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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 cell lines. METHODS AND RESULTS: We screened using a candidate chemical structure approach, a library of 400 steroid inhibitor drugs on 5 human glioma cell lines, and a normal human astrocyte cell line. We discovered 4 potent new drugs of the androsterone family that can induce significant death of glioma cells, (n = 5/5) within a 24-hour period and contrary to normal human astrocytes. 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 cell lines. 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 achieved. Nevertheless, radiotherapy is very useful when tumor site is not accessible and for patients with poor clinical condition. Radiotherapy is better tolerable than surgery, has minor complications, and provides acceptable survival. Biopsy might be useful to differentiate with benign processes when MRI is not convincing and to define-tumoral genetics for future use of targeted agents. MATERIAL AND METHODS: The characteristics of 26 patients aged ≥ 16 years with brainstem glioma diagnosed in our center between 1987 and 2005 were reviewed. RESULTS: The median age at diagnosis is 35 years, with a median survival of 30.1 months (range 4–237.5 months). The main presenting symptoms were cranial neuropathy, ataxia, and/or hydrocephalus. Diagnosis is mostly based on MRI findings. Histological diagnosis was available in only 8 of 26 patients. Contrast enhancement, central necrosis, or poorly delineated lesion on MRI correlate with poor prognosis (median survival of 23.1 vs 120.1 months). Three patients underwent a subtotal resection, but all 26 were irradiated with doses between 51 and 66 Gy. Three patients suffered from radiotherapy-linked complications consisting of necrosis (n = 1) and hearing disability (n = 2). Salvage chemotherapy was given in 5 patients at recurrence with a median survival of 15.7 months. The following patient features (characteristics) predict poorer prognosis: age above 40 years, hydrocephalus, WHO performance above 1 and high grade appearance on MRI. Duration of symptoms <3 months was almost statistically significant to predict poorer prognosis. The more negative prognostic features present, the worse the survival. This was statistically significant. CONCLUSIONS: The need to perform a biopsy is a matter of dispute. In our series, contrast enhancement, central necrosis, and poorly marginated lesions predicted shorter survival, indicating that radiological features can be used to diagnose high-grade glioma including biopsy is not necessary. All patients were irradiated with acceptable survival, only 3 suffered from complications. Radiotherapy alone is still an excellent therapeutic option. Age >40 years, long tracts signs, hydrocephalus, and WHO score >1 predicted for poorer prognosis. Shorter duration of symptoms was almost significant. This confirms the literature and can be used to decide which patients can benefit from more aggressive treatment. Chemotherapy should be preserved as rescue therapy at recurrence, seeing the median survival in our patient group.

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 chemo-resistance 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 cells established from surgeries (n = 2) and cell lines (n = 3), and a normal human neuroprogenitor 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 RADIOSCURITY FOR RECURRENT GLOBLASTOMA RESISTANCE TO THE TEMOZOLOMIDE
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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. Gammaknife radiosurgery (GK) 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 of 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. Histology 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 GK was 9.2 months (range: 6–11 months). The median target tumor size was 8.1 cm3 (range: 0.65–38.1 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.
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 < 0.001; 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 = 0.024) 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 = 0.1, they had a worse KPS before, P = 0.04, and after surgery, P = 0.02, and had more biopsies, 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 = 123) vs 216 days for women (n = 91), log rank P < 0.037. 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: 35 patients (24 males, 11 females; median age 63 years, range: 32–74 years), median Karnofsky performance status 70% (range 40–100), 21 primary cord glioblastoma, 14 secondary glioblastoma. Nine patients had a history of prior radiation therapy. Initial KPS demonstrated a median KPS of 50% at presentation. Median survival from initial diagnosis was 9.9 months, 2 patients (5%) died within the first month of presentation. A total of 22 patients had surgery (3 total resections) and 14 had a 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.087. CONCURRENT 3-TIMES DAILY ULTRAfractionated RADIATION THERAPy AND TEMOZOLomIDE FOR NEWLY INOPERABLE Glioblastoma: TEMoFRaC, A PHASE II STUDY
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BACKGROUND: Ultrafractionation radiation therapy consists in irradiating cells or tumor tissues several times daily, delivering low doses at which hyperfractionation has the potential to increase the tumoricidal capacity. This study was designed to evaluate the efficacy 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. Median follow-up for patients without progressive disease is 28 days. Tolerance and toxicity are the primary endpoints and survival, 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 open 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 bed 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 radiation therapy). 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 stereotopic 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 stereotopic 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 assay with microarray expression data to identify genes that could potentially be used to predict the response of glioblastomas to TMZ.
TMZ therapy. We first obtained the individual IC50 values for TMZ in 7 malignant glioma cell lines and then identified the genes whose expression correlated most highly with TMZ sensitivity employing a cDNA microarray. We present here a list of the most highly up- and downregulated genes which may be involved in conferring TMZ sensitivity/resistance in malignant gliomas including glioblastomas, although most of the genes have not been implicated as a causal factor in the TMZ response except MGMT. We have also demonstrated and confirmed the MGMT methylation status, quantitative MGMT mRNA levels, and MGMT protein expression levels in TMZ resistant glioma cells in vitro. Our results are thus consistent with previous studies and suggest that a dominant mechanism conferring sensitivity/resistance to TMZ exists in malignant glioma cells. Although the present study does have several limitations, our report on these genes could represent not only the potential molecular markers for TMZ sensitivity/resistance but also the chemotherapy targets. Furthermore, the present study could provide a foundation for alternative therapeutic strategies including novel combination treatments that incorporate additional reagents directed at overcoming resistance to TMZ.

**P.090. TEMOZOLOMIDE DOSE DENSE AS SALVAGE TREATMENT FOR GLIOBLASTOMA**

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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 one showed low toxicity and good efficacy. METHODS: We have retrospectively analyzed clinical data of 14 patients treated with TMZ-DD 150 mg/m2 1 week on–1 week off 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. The evidence of clinical improvement or/and neurological progression during TMZ-SS. All patients had a diagnosis of primary GBM: 11 were radically operated (78.5%) and 3 were submitted to partial exeresis (21.5%). MGMT status was as follows: unmethylated MGMT: 9 patients (64%) and methylated MGMT: 5 patients (36%). Eleven patients (78.5%) received concurrent chemo- and radiotherapy (RT) (Stupp regimen); 2 patients received radiotherapy (RT) only (14.3%); 1 for age and 1 for low PS (he received only 45 Gy palliative treatment). One patient (7.2%) was not submitted to RT for the extension of the disease (both frontal lobes). Adjuvant TMZ was given, or as primary treatment, all patients were submitted to TMZ-DD: median number of cycles delivered was 4 (range: 2–12 cycles). At clinical and/or neuroradiological investigations, all patients underwent TMZ-DD: 12 after the first progression (85.7%) and 2 patients (14.3%) for progression after second surgery. Six patients showed a disease control defined as the sum of objective response (1 patient with complete response) and stable disease (5 patients), with a median duration of response of 4.7 months (1–30 months); 3 patients (21%) were unmethylated and 3 patients were methylated (50%). One patient achieved the resectability after 3 months of TMZ-DD. Median progression free survival was 3.4 months. Median overall survival was 12.3 months (range: 9–39 months). No grade 3–4 toxicity (CTC 3.0) was recorded: 4 patients presented hematologic toxicity (G2) and 1 skin rash (G2). CONCLUSIONS: TMZ-DD is feasible and may be a good option after failure of TMZ-SS for its good safety profile. Its role as neoadjuvant treatment might be further investigated.

**P.091. HYPFRONPARNATED HIGH-DOSE IRRADIATION PLANNED BY METHIONINE PET FOR THE TREATMENT OF GLIOBLASTOMA 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 and without MET-PET. MATERIAL: MATERIAL: 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 patterns. GTV-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 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 among the patients experiencing grade 60. No patients experienced grade 3 toxicity among the patients experiencing grade 70. 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 a 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 adjusted to the routine care of patients with epilepsy, taking into account all clinical 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 treatment failure were defined as the primary endpoints. 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 in seizure frequency compared with baseline. 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
P.093. AGGRESSIVE TREATMENT IS APPROPRIATE FOR ELDERLY (70 YEARS AND OLDER) PATIENTS WITH GliOMA 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 combined chemotherapy, radiation, and surgery 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. OS was the primary endpoint of this retrospective study. Univariate and multivariate analyses were performed, utilizing the log-rank test and Cox proportional hazards model to assess the difference in survival for patients with various characteristics and treatment. RESULTS: Two hundred and six patients 70 years of age and older were identified from the database. The median age was 75 years (range: 70–90 years). Patients had a wide variety of treatment modalities ranging from no treatment to a combination of surgery with chemoradiation with temozolomide. Median OS was 4.5 months. In univariate analysis, factors that significantly affected OS included Karnofsky performance status (KPS) (P < 0.001), age at diagnosis (5.1 months for age 70–79 vs 3.1 months for age 80 or greater, P < 0.001), and the extent of disease with patients with bilateral disease (P = 0.003), multifocal disease (P = 0.02), and multicentric disease (P = 0.002) doing worse in all cases. Patients treated with radiation had longer OS of 6.7 vs 1.9 months for those not treated with radiation (P < 0.001) as did patients treated with chemotherapy who had an OS of 11.2 vs 3.5 months for those not treated with chemotherapy (P < 0.001). On multivariate analysis, higher KPS (P = 0.006), surgical resection (P < 0.001), radiation (P < 0.001), and chemotherapy (P < 0.001) were all found to be independently associated with improved OS. CONCLUSIONS: These data suggest that aggressive treatment with radiation, chemotherapy, and surgery improves OS in patients 70 years or older with newly diagnosed GBM.

P.094. TRABEDERSEN IN RECURRENT HIGH-GRADE GLIOMA: 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, multinational 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 145 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 (AA, WHO grade II or GBM, WHO grade IV) 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 and 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 or PR + 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 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 HGG. On the basis of the phase IIb results, the pivotal phase III study SAPHIRE 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 GliOMASTOMA MULTIFORME 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 chemotheraphy, MRI, 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 60 (range: 16–72), 43 were males. The median follow-up was 12 month (range: 2–37). The MRI 1 month after the end of radiotherapy showed progressive enhancement in 35 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, the pivotal phase III study, 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. OS 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 < 0.0013) and a trend toward better overall survival for patients with PSP but it did not reach statistical significance (P = 0.08). These data support the notion to continue TMZ in the case of progressive lesions immediately after TMZ radiotherapy. Further research is needed to establish reliable imaging patterns that distinguish between REP and PSP.

P.096. SALVAGE THERAPY AFTER FAILURE OF FIRST LINE TREATMENT FOR GliOMASTOMA MULTIFORME

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Concomitant chemoradiotherapy is a mainstay 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 126 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 rechallenged 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 bevacisumab and irinotecan). Overall median survival was 16.6 (SD 1) weeks, in patients receiving best-supportive care it was 7.1 (SD 3.2) 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 semi-quantitative O'-methylguanine DNA methyltransferase (MGMT) promoter methylation status to diagnose the pseudo-progression, which is a major diagnostic dilemma in modern treatment protocol involving concurrent chemotherapy 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 compared with those of methylation-specific polymerase chain reaction (MSP) and the protein expression of gene product. Correlation between those molecular signatures and clinical outcome was analyzed. In case of radiological progression after chemoradiotherapy, the sensitivity and specificity of the MS-MLPA was 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 translocation. 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-AMINOLEVULINIC 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] fluorothymidine positron emission tomography (PET) was investigated. METHODS: Fluorescence tissue margins were mapped intraoperatively by neuroravigation 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 affinity tumor parts, which was verified by contrast MRI scans without ALA 24 h after surgery. MRI and FET–PET uptake was demonstrated only in one patient as a small residual spot. PET–FET 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 multifocal 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. MRS, 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 Vcw, Vth, Ktrans, and Vh. Regression analysis beyond day 15 was 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: highest pronounced inter-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. DIFFUSION 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 and Vh 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 trend 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.

P.100. MULTI-PROFESSIONAL, PRE-TREATMENT ASSESSMENT CLINIC FOR PATIENTS WITH GliOBLASTOMA RECEIVING CONCOMITANT CHEMIoRADIOTHERAPY

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BACKGROUND: The investigation and management of patients with glioma is increasingly complex with the introduction of routine biomarker profiling, multimodality care, and complex protocols for clinical trials. Delays in starting nonsurgical treatments can be deleterious and should be minimized. The need, therefore, for patients rapidly to understand the issues and make complex decisions is paramount. We have introduced a multidisciplinary Pre-Treatment Assessment clinic (PTAC) into routine practice to improve the patient’s illness related education, optimize therapeutic strategies, minimize symptoms and collateral entries. METHODS: Following surgery, patients with newly diagnosed primary brain tumors are assessed by a Consultant Oncologist and a Clinical Nurse Specialist (CNS) in a Neuro-Oncology outpatient clinic. During this consultation, the patient is informed of their diagnosis and proposals for further treatment are discussed. This consultation has been shown to be traumatic and ineffective in terms of information transfer and decision-making. The next contact between patient and specialist team was not normal until the start of radiotherapy planning, several weeks later. Patients now attend the new PTAC 1–2 weeks following their initial consultation. This innovative clinic is led by the same CNS as attended the initial consultation and a Specialist Therapy Radiographer. There is access to medical, psychological, and complementary therapy advice. Advice for the involved professionals has been developed and clinical supervision is provided by Neuro-Oncology Consultants. The PTAC addresses issues of patient and carer education, psychological adaptation, symptom control, the ongoing appropriateness of the therapeutic strategy, detailed
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 the 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. The survival 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 adjunct to successful surgical excision of 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 this series. Tumor localization was done using intraoperative 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 8 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 resection and performed an aimed coagulation without traumatizing 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 neuronavigation, intraoperative neuronavigation technique with laser thermodestruction allow maximal safe resection of tumor that predict higher levels of quality of life in patients with brain gliomas in eloquent area. 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 the termination of leviteracetam. 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 (PFS) was 18%, 5 months overall survival was 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.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. Performance Status 70%; 9 patients were treated for a second recurrence. The combination was tested to combined near-continuous temozolomide (50–60 mg/m2 day 1–21 or 50 mg/m2 day 1/5/7) plus weekly low-dose CCNU (40 mg fix dose at day 6/7). METHODS: A total of 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 the termination of leviteracetam. 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 (PFS) was 18%, 5 months overall survival was 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. RADIOTHERAPY 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 O(6)-methylguanine-DNA-methyltransferase (MGMT) promoter 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 70 were treated with radiotherapy (total of 60 Gy in 30 fractions) and TMZ (75 mg/m2/day), followed by continuous 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 neuroepithelial and 1 patient had grade III thymoblasticytoma and 11 patients had grade III/IV lymphoblasticytoma. 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 leucopenia, 3 had grade 3 asymptomatic thrombocytopenia, and 1 patient had grade 3 leucocytopenia. But only 1 patient out of 75 was treated 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. We were able to finish the planned protocol. CONCLUSION: Hematotoxicities are less frequent 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 transport mechanisms, chemoresistance, and several signaling cascades/molecules (e.g., 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 H2 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 parallelled 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 p56, 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-coiled domain and pS6, were detected in immunoprecipitates from MVP-overexpressing cells. Furthermore, reduced dose of temozolomide was administered because of the onset of piaspinin. In the adjuvant phase, we preferred to administer 12 cycles of temozolomide instead of the standard 6 months regimen. In the majority of patients (90%), we adopted a modified schedule (150 m²/day 1–3, 75 mg/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 Gliald wafer placed were in the cavity), and 100% 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 neuropsychologic 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.106. A FIVE-YEAR FOLLOW-UP EXPERIENCE IN NEWLY DIAGNOSED Glioblastoma MULTIFORME

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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. Numerical 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 (CPT 11) 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 CPT 11 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 non-enzyme-inducing antiepileptic drugs (NEIAEDs) prior to receiving CPT 11. 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 weighed 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 DVT's and 2 PE's requiring IVC filter placement, 2 intracranial hemorrhages and a femoral vein thrombosis. All patients treated a clinical benefit and were taken off steroids rapidly after starting bevacizumab regardless of radiological response. Clinical and radiographic responses correlated well. Failures were mostly local progression in 12 cases, infiltrative nonenhancing (glioma-like) in 10 cases and multifocal including subependymal and leptome- ningeal in 8 patients. CONCLUSION: Bevacizumab-based regimen for relapsed GBM demonstrates superior activity when compared with historical treatments. It is safe and improves overall quality of life in this patients' category. Our results were as favorable as previously despite lower KPS on enrollment, and using lower doses of bevacizumab.
Early Initiation of Radiotherapy Plus Concurrent 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 concurrent 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 days/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 influenced OS in the young age group (biopsy vs complete: P = 0.06), but not in patients (P > 0.5 years (P = 3)). CONCLUSION: As the 12 of 24-month OS in our patients >65 years (median 57 years) and 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.

Phase II Study of Ifosfamide, Carboplatin, and Etoposide in Patients with a First Recurrence 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 prolongs 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 recurrence 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 at 6 months after the ICE treatment (PSF-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 grade 3–4 toxicity, there being no grade 5 toxicity. CONCLUSION: Although the overall median survival was 17 weeks (95% CI 10–24 weeks), the response rate was high (25% (95% CI 9–34%)). The median progression-free survival was 17 weeks, however, grade 3–4 toxicity has only been reported in 12% of patients. The aim of the study was to investigate the factors involved in thrombocytopenia in a cohort of glioblastoma (GBM) patients treated with standard protocol.

Introduction: Seizures in brain tumor patients are a common event. Tumoral epithelium treatment guidelines based on clinical studies are scarce. Knowledge on hematological effects of antiepileptic drugs (AEDs) in this population is limited. Thrombocytopenia is a recognized side effect of valproate (VPA) in antiepileptic drug (AED) therapy of temozolomide-resistant GBM. However, grade 3–4 toxicity has only been reported in 12% of patients. The aim of the study was to investigate the factors involved in thrombocytopenia in a cohort of glioblastoma (GBM) patients treated with standard protocol.

Material and Methods: We reviewed 101 newly diagnosed GBM patients treated with Stupp schedule until July 2009, from 2 institutions database. Clinical data, presence of seizures, use of AEDs, platelet count, and accumulated TMZ dose were analyzed at each cycle. AED treatment was categorized as follows: VPA (alone or combined with non-enzyme–inducing AEDs), LEV (levetiracetam), enzyme-inducing AEDs (alone or in combination with other AEDs) and non-AEDs users. Thrombocytopenia was operationally defined both as a continuous platelet count and as a dichotomous variable (cut-off 100 × 10^9/L) aimed at detecting effects on clinical decision-making. A linear and a probit pooled cross-sectional regression analysis, respectively, were used to study the impact of covariates on thrombocytopenia. RESULTS: Thirty-five (35%) patients presented seizures at onset and it appeared during follow-up in 18 (27%). Five (9.4%) and 2 (3.8%) patients needed 2 and 3 AEDs to control seizures, respectively. Thrombocytopenia was observed in 37% of all GBM patients. Grade 3–4 thrombocytopenia was found in 11%. Decrease in platelet count was related with TMZ dose (P < .001), age (P < .001) and VPA (P = .004). Platelet count < 100 × 10^9/L was only associated with TMZ dose (P = .001). Age (P = .08) and VPA (P = .12) lost their influence. AEDs were not associated with time to progression (TPP), being RPA prognostic class the only variable with significant impact on TPP in Cox regression analysis. CONCLUSION: Accumulated dose of TMZ was the main determinant factor of platelet count and of thrombocytopenia. Although VPA and age were also factors associated with decreasing platelet count, thrombocytopenia modifying clinical management was only significantly related with TMZ. The lack of significant age-related effect on platelet count and on the risk of thrombocytopenia may suggest that healthy elderly patients tolerate TMZ-related side effects better.
of VPA effect on critical thrombocytopenia for treatment decision-making could be related with the sample size of this study.

P.114. IDENTIFICATION OF CD133+/TELOMERASE-LOW PROGENITOR CELLS IN GLOBLASTOMA-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 380 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+ and T2, FLAIR sequences); available results of amino-acid PET scan imaging were used to assess the metabolic response. 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%); 1 of 14 patients (7%) 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 makes anti-angiogenic therapies 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 (TRAQ-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. Known and novel candidate proteins have been identified. On the basis of their expression profile and established literature knowledge, we have selected a dozen of proteins for which the differential expression in angiogenic gliomas was validated by quantitative PCR. For functional analysis, we are currently targeting these genes using small interfering RNAs (siRNA) to specifically knockdown the proteins in various glioma cell lines, including glioma stem cell-like cells. The transfected cell lines are analyzed with regard to their proliferation rate, migration capacity, invasiveness, and clonogenic potential. Tube formation in siRNA-treated HUVEC endothelial cells is measured to evaluate the effect of the proteins on angiogenesis. Complementary data are obtained by overexpression studies of the selected proteins. We will report on the functional involvement of new candidate proteins in glioma angiogenesis, 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 GLOBLASTOMA: 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 phase II study on bevacizumab plus fotemustine in GBMs recurrent after standard treatment (surgery, radiotherapy, and temozolomide). PATIENTS AND METHODS: Fifty-nine patients (38 males and 21 females) with a median age of 58 years (range 24–78), and a median KPS of 80 (range 60–100) were enrolled in a phase 2 protocol with bevacizumab at 10 mg/kg on day 1, 15 and fotemustine at 75 mg/m2/day on day 1, 8 (induction phase) and, after 3 weeks interval, bevacizumab at 10 mg/kg and fotemustine at 75 mg/m2 every 3 weeks as a maintenance. Treatment was maintained until tumor progression or unacceptable toxicity. MRI was performed at baseline, after the induction phase and thereafter every 2 months. Response was defined as a reduction of enhancement on T1-weighted images associated with stability or reduction on FLAIR images (according to recently modified Macdonald’s criteria). Primary end-point was 6-month progression-free survival, whereas secondary endpoints were response rate, overall survival, and safety. RESULTS: The 6-month progression-free survival was 32% and median survival time was 6.7 months (range: 1.2–18+). The overall response rate was 43.4%, with 43.4% complete responses, 8.6% major partial responses, 30.5% partial responses, and 41% stabilization. Maximal responses were precocious, after the induction phase. Steroids were reduced or stopped in 61% of
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 hyperton with reversible hypertensive encephalopathy; hemorrhagic events (12.5%) (2 lobar hemorrhages, 2 asymptomatic intratumoral bleedings, 1 esophageal 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 for the UK comprised 6 weeks 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 methylation 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
K. Elandt1, M. Preusser1, K. Dieckmann2, J. Hainfellner3, M. Hassler4, and P.119. TREATMENT WITH MULTIKINASE INHIBITOR SORAFENIB FOR RECURRENT CENTRAL NERVOUS SYSTEM TUMORS
K. Elandt1, M. Preusser1, K. Dieckmann2, J. Hainfellner3, M. Hassler4, and
1BHOC, Bristol, UK; 2Southmead Hospital, Bristol, United Kingdom; 3Southmead Hospital, Bristol, UK
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 hemangiopericytoma, and 1 hemangioblastoma. 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 progression (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 3 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 hemangioblastoma 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 gastrointes-tinal 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 in our patient cohort. CONCLUSION: Multikinase inhibitor sorafenib showed responses in heavily pretreated patients with recurrent CNS tumors.

P.120. ACTIVATION OF P53 BY MDM2 ANTAGONISTS DOWN-REGULATES SURVIVIN AND INDUCES CYCLE ARREST AND APOPTOSIS IN HUMAN GLIOMA TUMOR CELLS
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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 hemangiopericytoma, and 1 hemangioblastoma. 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 progression (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 3 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 hemangioblastoma 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 inhibi-tors or with antihypertensive combination therapy. More than 10 patients had skin changes similar to hand-foot syndrome grade II–IV. One gastrointes-tinal 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 in our patient cohort. CONCLUSION: Multikinase inhibitor sorafenib showed responses in heavily pretreated patients with recurrent CNS tumors.

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 oligodendrogloma, 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 fotemustine in a limited number of cases; all the patients presented 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, or subtotal), and in 8 cases, during the same procedure, intratumoral CT wafer 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 post-operative 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 high used streptostereic radiatherapy has also been performed. In 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 GLOBLASTOMA MULTIFORME RECURRENCES

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Glioblastoma multiforme (GBM) is the most frequent form of brain tumor and the most malignant astroglial neoplasm. GBM comprises 15%–20% of all primary intracranial tumors and is ≥60% of astrocytic neoplasms. The incidence is in the range of 3–4 new cases per 100,000 population per year. It typically affects 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 survival time is limited. The clinical and radiological signs are the only possible criterium of 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 5 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 surgery indications, and also to achieve the planning of general treatment strategy. We would like to point our treatment strategy for recurrent GM out 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 ≤ grade 2; (b) only local relapse, without multifocality; (c) possibility of cytoradical resection of the mass ≥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, immunohisto logical, and cytogenetic investigation. Selected patient’s group benefit from recurrent GM surgery supplemented by adequate subsequent oncotherapy that 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 every subgroup. Surgery independent 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 of AC results in recurrent glioma, this treatment has widely been used and seems improved some survival benefit. The MRI evaluation is a standard practice to follow the treated patients. 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 4 months to separate the tumor and its clinical outcome in recurrent high-grade or transformed glioma.

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 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 paraffin-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 was present between the tumor cells, and granular cells with ballooned...
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. 

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, 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. Tmz 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 volumes 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 early illness experience. An important theme to emerge involved the participants describing what they found difﬁcult about the way 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 clearly deﬁned. 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 the radio-chemotherapeutic agents. MATERIALS AND METHODS: We studied 18 patients affected by ﬁbrellary 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 chirurgical 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, 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 IDHI 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 investi-gated 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 hetrozygosity 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 methyl-ation status becoming methylated.

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Intracranial chemotherapy is a crucial element in the treatment of leptome- ningeal 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 antangiogenic chemother- apy. Since May 1998, patients received intracranial etoposide at a dose of 0.25–0.5 mg x 5 days every 2–6 weeks for a total of 306 courses (1–41 per patient) via an Ommaya reservoir. Intracranial methotrexate and mafos- famide 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 intensely 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 resist- ance 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), meninigitis (n = 2), and visual disturbance (n = 3), which were connected to benign cerebral hyper- tension in 4 children that improved after one time of pressure release by lumbar/intraventricular CSF removal. Etoposide was generally well toler- ated, although mild toxicities occurred (headache, n = 2; nausea/vomiting, n = 2). Since all patients received some sort of concurrent anti-cancer therapy, the efficacy of intracranial 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 (pinealear suprasellar) in Caucasians. Paraaxial tumors are mostly reported in Asiatic 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 a diplopia with raised intracranial pressure, requiring ventriculo- cisternostomy. The MRI showed a localized pineal tumor associated with raised seric bHCG (700 UI/L). The treatment included chemotherapy (BEP) + 50 Gy focal radiotherapy. A progressive visual loss occurred 6 years later, with unilateral swelling of optic nerve. Pure germinoma was confirmed by biopsy. A 34-year-old male presented a diminution of vision predominantly on the right side, a left lateral hemianopsia, and a bilateral atrophy of the optic nerves. 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 boy presented headache, diabetes insipidus, a growth hormone deficit, a bilateral diminution of vision, and bilateral optic atrophy. MRI showed a pineal region tumor. CSF HCG was raised (90 UI/L). This “biologic” secreting tumor was treated according to GCT 96 SIOP protocol: chemotherapy (Etoposide ifosfamide and Carboplatin) followed by 54 Gy radiation of hypothalamus and pineal region. He relapsed 6 years later as a ventricular seeding with chiasmatic, right optic nerve bulbar and pituitary localizations. AFP and HCG were elevated in CSF and serum. All 3 patients are currently in second remission (45.5%); CR in 4 patients, PR in 6 patients, SD 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%). median of age: 59%); 1 patient with CR died in remission in 1.5 month after finishing therapy from leuкоencephalopathy. 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 leuкоence- phalopathy. Combination of bevacizumab and irinotecan is an effective treatment in relapsed pediatric GB with acceptable toxicity. PFS in this group is higher than in patients with AA, what statistically proved (P = .05).

P.131. RESULTS OF TREATMENT PEDIATRIC RECURRENT HIGH-GRADE GLIOMA (HGG) WITH COMBINATION OF BEVACIZUMAB AND IRINOTECAN
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Recurrent HGG in children have 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 antangiogenic therapy, bevacizumab, and a cytotoxic agent, irino- can, 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 temozolo- mide. Relapse was documented by CT/MRI/PET. Median of follow-up was 6 months (range 2–17 months). In 19 patients (86.3%), the glioblastoma (G) was histologically verified, and in 3 patients (13.7%) anaplastic astrocytoma (A) was verified. Karnovsky was 50–100 (with median 80). All patients received 6-week cycles of combined therapy: bevacizumab 5 mg/kg/week + Irinotecan, and 29 mg/kg/week of both together with anticovants, 340 mg/m²/day (1), 8, 2, 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) was observed in 10 patients (45.5%); CR in 4 patients, PR in 6 patients, SD 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%). median of age: 59%); 1 patient with CR died in remission in 1.5 month after finishing therapy from leuкоencephalopathy. 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 leuкоenceph- alopathy. Combination of bevacizumab and irinotecan is an effective treatment in relapsed pediatric GB with acceptable toxicity. PFS in this group is higher than in patients with AA, what statistically proved (P = .05).

INTRODUCTION. Anaplastic astrocytoma (AA) is a rare tumor of CNS in children, which differs from the adult counterpart due to its surgical treatment perform- ment. 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 radio- therapy (RT), 25 pts - complex treatment (combination of resection, RT and chemotherapy (CHT)). Total resection of a tumor performed in 15 pts, sub- total - in 7 pts, partial - in 12 pts, biopsy - in 33 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 ± 8% and 50 ± 9

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% respectively. Medians of PFS and OS-24 and 60 mths respectively. PFS in pts with total resection was 69%, sub-total - 42%, partial - 10%, biopsy - 0% (p = 0.01). 5-year PFS was 56% in pts with complex treatment, 10% in pts after surgical treatment and RT or surgery alone (p = 0.02). In pts under 5 years PFS - 80%, older 5 years - 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 treatment 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.133. MARKED REGRESSION OF CERVICAL PARAGANGLIOMA WITH ANTIANGIOGENIC METRONOMIC THERAPY
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BACKGROUND: Paragangliomas of the head and neck are usually benign, hypervascular neuroendocrine tumors of the autonomic nervous system. Management is difficult, because such tumors are often inoperable and radiotherapy remains controversial, especially in young age. CASE REPORT: A 15-year-old girl was admitted to our hospital with a cervical mass. Imaging revealed bilateral paraganglioma, deemed inoperable because of location and size. The patient was observed with repeated MRI studies. After 12 months, the patient showed remarkable reduction of tumor mass and the palpable cervical mass decreased.

METHODS: Antiangiogenic therapy was initiated with daily oral thalidomide 100 mg, augmented with biweekly intravenous bevacizumab 10 mg/kg.

RESULTS: Our patient showed an impressive response to therapy. After 8 weeks, MRI revealed response to treatment with regression in size and cervical necrosis. Additionally, the palpable cervical mass was not present any more. Therapy was well tolerated, and side effects included lymphopenia and peripheral neuropathy, requiring dose reduction of thalidomide and switch to lenalidomide after 1 year. With ongoing therapy, the patient could continue school. CONCLUSION: Antiangiogenic therapy may present a promising approach in cervical paraganglioma.

MENINGIOMAS

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 (33%), followed by clival and petroclival regions (16%). Forty-five percent of the patients 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.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 II, and 8% (4 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 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.137. INTRACRANIAL MENINGIOMAS WITH LEPTOMENINGEAL DISSEMINATION
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PURPOSE: Intracranial meningiomas comprised of 15%–20% of all primary brain tumors. The spread of meningioma through cerebrospinal fluid (CSF), although very rare, was reported primarily in nonbenign subtypes. The authors report rare cases of meningioma with leptomeningeal dissemination (LD) after surgery. METHOD: Four females (age ranged 21–72 years, mean 56.5) of 332 consecutive patients (1.2%) with surgically resected intracranial meningioma manifested CSF dissemination. The initial tumor location was posterior fossa in 2 cases and lateral ventricle and parasagittal convexity in 1 case each. Pathological examination revealed 2 cases of WHO grade II and 1 case of grade I and III, respectively. All patients received Simpson grade I/II resection at the first operation. Adjuvant focal radiotherapy was performed in a case of atypical meningioma with Simpson II resection and a case of malignant subtype. RESULTS: Each LD occurred after the first operation with the time interval of 2.5 months–6.9 years. A patient with malignant subtype showed the shortest time to LD. Metastasis was confined to intracranial CSF space in 2 patients, and was extended to both cranial and spinal subarachnoidal space in 2. One patient also showed multiple extraneural metastases. Treatment included decompressive surgery for rapidly progressive motor weakness in 3 patients and radiosurgery with or without focal radiotherapy in 2. Three patients showed disease progression with the survival ranged from 1 month to 3.5 years after LD. One patient with WHO grade I meningioma was alive in stable disease at the time of last follow-up. CONCLUSION: LD of meningioma after surgery is very rare; however, it should be considered as a cause of unusual presentation. Further study for more effective systemic and local treatment for patients with CSF disseminated recurrent meningioma is needed. Whether surgery is the iatrogenic cause of metastasis of meningioma is further needed to be discussed.

P.138. IMPROVED PREDICTION OF TUMOR RECURRENTITY IN MENINGIOMAS WITH INTRATUMORAL CYTOGENETIC HETEROGENEITY
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OBJECTIVE: 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 5% of the cases, they turn into malignant forms with aggressive clinical behavior and increased risk of tumor recurrence. METHODS: Meningiomas are cytogenetically well characterized, with normal karyotype or monosomy of chromosome 22 in most tumors and clinically relevant secondary losses of other autosomes in a subset of potentially malignant tumors. The order of accumulating genetic aberrations has previously been estimated with oncogenic trees models, and a genetic progression score derived from these models was shown to be predictive for tumor recurrence. RESULTS: Although more homogeneous than other cancer types, meningiomas show considerable intratumoral cytogenetic heterogeneity, particularly in their malignant form. We observed different cytogenetic patterns in tumor cells of 221 out of 661 (33.4%) meningiomas. The present investigation demonstrates that it is not sufficient to consider only the most frequent cytogenetic pattern observed in a set of cells derived from the same tumor. CONCLUSION: Even a single clone with more advanced genetic progression also indicates clinical progression. Cox regression analysis reveals that the clone with most advanced progression is a superior marker for recurrence in meningiomas. It is expected that for other cancer types with higher intertumoral heterogeneity the selection of single genetically advanced cells improves the prediction of clinical tumor progression in an even more drastic manner.

P.139. TREATMENT OF RECURRENT MENINGIOMAS WITH IMATINIB MESYLATE: A SINGLE-INSTITUTION EXPERIENCE
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BACKGROUND: Some irresectable and symptomatic meningiomas 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 meningiomas can be deemed as insufficient. Because of the prevalent expression of PDGF receptors in meningiomas, 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 meningiomas, 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 above-mentioned 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. Out of 9 patients treated with imatinib, 7 had stable disease and 2 progressed at the first scan after almost 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 3–31 months). Interestingly, imatinib treatment had a favorable impact on overall survival of meningioma patients (log-rank test, P = 0.034). CONCLUSION: Single-agent imatinib mesylate is a well-tolerated therapeutic option with a high rate of disease stabilizations in recurrent meningiomas. 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 meningiomas, particularly in lack of other therapeutic options.

P.13 SPINAL CORD TUMORS

P.140. EPENDYMOMAS OF THE FILUM TERMINALE: A SINGLE-INSTITUTION EXPERIENCE

BACKGROUND: Filum terminale ependymomas form a specific variant of spinal cord tumors. Histologically, most are myxopapillary (WHO grade I), although grade II tumors also occur. Controversy exists about the role of surgical removal (total vs subtotal) and technique (‘en bloc’ vs piecemeal) and about adjuvant radiotherapy. METHODS: We performed a retrospective analysis of 22 cases treated from 1992 until 2008 (average follow-up 64 months). Possible prognostic factors (dimensions, metastasis, surgical aspects, and radiotherapy) were analyzed. RESULTS: In 3 patients, metastases were found at diagnosis. Surgery was complete in 18 (including 2 with metastasis resection, in 3 on ‘en bloc,’ the others piecemeal), partial in 4. Histology showed myxopapillary type 16 (4 metastasized), grade I in 6 (1 metastasized). Adjuvant radiotherapy was performed after incomplete resection and/or metastasis. Delayed radiotherapy was given in 2 cases after local recurrence and was given in 2 on a metastasis. At last follow-up, 1 patient died of progressive disease and 1 died of unrelated cause (tumor free). Five patients were treated for recurrence. Of the 20 patients alive, 17 were tumor free and 3 had stable disease. The most important prognostic factor was initial tumor presentation: all 9 tumors smaller than 4.5 cm did not have metastasis or recurrence, were not irradiated, and had excellent functional outcome. In larger tumors, there were more metastases and recurrences, radiotherapy was performed and functional outcome was worse. CONCLUSION: Initial tumor characteristics, associated with the possibility to obtain complete surgical resection, are more important than histology or factors influenced by treatment.
P.141*. SPINAL CORD COMPRESSION FROM NEUROFIBROMAS IN NEUROFIBROMATOSIS TYPE 1 PATIENTS
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INTRODUCTION: Neurofibromas are characteristic tumors of Neurofibromatosis type 1 (NFI). They arise as discrete or more diffuse plexiform tumors, growing along cutaneous and subcutaneous nerves and spinal roots. Spinal neurofibromas are present in at least 50% of NFI 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 NFI 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 NFI patients, followed up, and treated in a neurofibromatous 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 noted. 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 patients at presentation ranges of 29 to 51 years, Clinical presentation was quadriaparesis 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 osteoelastic laminotomies. Five surgical events were followed by an upgraded performance, with full recovery in 2 from 4 patients. One patient, suffering from a long-standing severe quadriaparesis, still presents a severe deficit. In no cases the tumor recurred or progressed after surgery. No kyphotic deformity was observed at follow-up. CONCLUSIONS: Spinal cord compression secondary to spinal root neurofibromas is a known but infrequently reported complication in NFI. Spinal cord 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.

P.142. PARAGANGLIOMA OF THE CAUDA EQUINA: A REPORT OF 3 CASES
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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 paraganglia cells in the central nervous system remains a point of debate. There is 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. Surgical resection of CEP improves local control symptoms and results in stability in 12 (84.6%), and clinical deterioration in 1 from I to II functional

P.143. MALIGNANT SPINAL CORD COMPRESSION IN A PATIENT WITH GLIOBLASTOMA
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INTRODUCTION: Spinal metastases in patients with malignant gliomas are rare, but a well-known complication in the advanced stage of the disease. Literature on the treatment of malignant spinal cord compression in patients with malignant gliomas is limited. CASE REPORT: A 65-year-old female patient was diagnosed with glioblastoma in July 2008. After gross total resection, she received a standard concomitant radiochemotherapy according to the STUPP protocol. At first local relapse 10 months after diagnosis, she was treated by gamma-knife and subsequent, dose-intensified temozolomide chemotherapy. Fourteen months after diagnosis, she was admitted because of an acute deterioration of gait function within 48 hours. Neurological examination revealed a paresis of the right leg. Clinically, the neurological deficit was attributed to a progressive left temporal glioblastoma. On the next day she developed a lower limbs. Cralial MRI showed a multicentric bilateral glioblastoma. When compared with the previous MRI scan 2 months ago, multicentric supratentorial tumor progression in the left and right hemisphere could be detected, but not compatible with neurological signs and symptoms. MRI of the spinal cord exhibited contrast-enhancing lesions at the spinal level T3/4 and T6/7. Although steroids were administered and acute local radiotherapy (5 x 4 Gy) was applied, no improvement in neurological function could be achieved. Urinary and anal incontinence as well as diffuse abdominal pain occurred. Considering the progressive disease, no further antitumor treatment was started and the best supportive care was established at discharge. CONCLUSION: Reviewing the literature, in glioblastoma patients with malignant spinal cord compression, local radiotherapy can provide a temporary relief from pain and mild improvement of neurological deficits without survival advantage. However, no evidence-based treatment guidelines are presently available. Although our patient did not benefit from the therapeutic interventions, an early diagnosis and subsequent treatment seems mandatory to prevent loss of neurological function.

P.144. SPINAL CORD AND BRAINSTEM HEMANGIOBLASTOMAS IN PATIENTS WITH VON HIPPEL–LINDAU DISEASE: MICROSURGICAL RESULTS IN A REFERRAL CENTER SERIES
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INTRODUCTION: Spinal cord hemangioblastomas make up for 5% of primary spinal cord tumors, and are associated with von Hippel–Lindau disease (VHL) in more than 75% of cases, where they can be found at multiple levels. Brainstem hemangioblastomas are present in up to 20% of VHL patients, and their discovery is almost pathognomonic of the disease. Management of these tumors is controversial, having in mind that these patients are not affected bearers of isolated hemangioblastomas, but are affected by a genetic multisystem disease. The aim of this paper is to present the microsurgical management results of spinal cord and brainstem hemangioblastomas in a VHL referral center. MATERIALS AND METHODS: We reviewed a series of 11 patients (mean age 40 ± 15.4 years, range 21–66 years) who underwent 13 operations to remove 17 hemangioblastomas: 3 in brainstem, 3 in the bulbo-medullary junction, 4 cervical, 6 thoracic, and 1 lumbar hemangioblastomas. All surgical procedures were performed by the same neurosurgeon (JMdC) in a VHL referral center. The indication for surgery was established by the appearance of clinical symptoms or evident growth of hemangioblastoma. RESULTS: Sensory deficit was the most frequent symptom, present in 10 patients (76.9%), followed by motor deficit in 7 (53.8%). Complete resection was possible in all cases. In the pre- and postoperative functional assessment, according to McCormick’s scale, clinical stability in 12 (84.6%), and clinical deterioration in 1 from I to II functional
grade (7.7%). Early in the postoperative assessment, a functional deterioration occurred in 4 (30.8%) patients, all fully recovered after 3 months, except in the abovementioned case. CONCLUSIONS: Complete microsurgical resection of spinal cord and brainstem hemangioblastomas in VHL patients can be achieved with good surgical results and a very low rate of neurological complications, when performed in a VHL referral center with surgeons particularly involved in the management of patients with this disease.

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 (BLL), 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 BLL 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 a complete remission 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 treated by ASCT from an HLA identical sibling. Evolution was characterized by paraparesis. Immediate diagnosis is of major importance as evolution is poor, even with intensive 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.148*. CENTRAL NERVOUS SYSTEM (CNS) COMPLICATIONS OF MYELOMATOUS MENINGITIS AFTER ALLOGENIC STEM CELL TRANSPLANTATION (ASCT)
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INTRODUCTION: Neurologic manifestations are not uncommon in multiple myeloma (MM). They are represented by a broad spectrum according to the differences in pathological mechanisms, clinical presentation, and therapy. PURPOSE AND METHODS: We report a case of a 30-year-old Caucasian male who underwent chemotherapy and ASCT that controlled the disease for a number of years. For headache complaints, he underwent diagnostic procedures that established the leptomeningeal 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 treated by ASCT from an HLA identical sibling. Complete response 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 involvement and started an intrathecal chemotherapy regimen with combination therapy for central nervous system by MM.

P.149*. THE ROLE OF TEMOZOLOMIDE FOR PATIENTS WITH METASTATIC BRAIN DISEASE
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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 included in this study. Patients with BM from NSCLC (21 patients), melanoma (17 patients), and BC (17 patients) were treated with WBI (3 Gy/30 Gy) and concomitant TMZ therapy (75 mg/m²/day orally on Days 1–14). Patients with BM from NSCLC (7 patients), melanoma (17 patients) were treated with TMZ (150 mg/m²/day orally on days 1–5, every 4 weeks) as monotherapy. Eleven heavily pre-treated NSCLC patients [after 1–II lines of chemotherapy (and/or WBI)] were treated with combined chemotherapy of I (250 mg/m²/day intravenously, 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 + WB1-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 + WB1 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, 2 (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 + WB1 patients with NSCLC brain metastases, 7 (63.6%) SD, mOS was 8 months. In the TMZ + WB1 patients with melanoma brain metastases, 2 PR, 4 SD, 1 patient progressed. The mOS was 8 months. CONCLUSIONS: TMZ with WB1 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 WB1 in heavily pre-treated 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.

A significant difference in OS between RPA classes (3 years, 54.0, 46 months), 4.0, and 6.0 months, respectively. There was a significant difference 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 BC and SD, 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 LC. The median PFS was 5.0 and 3.0 months for BC and SD, 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 LC. 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 BC and SD, 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 LC.

BACKGROUND: Methotrexate (MTX) is an important chemotherapeutic agent in the management of oncological 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 mimic 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 intrathecal 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 leukemia receiving systemic low-dose MTX, cytarabine, cyclophosphamide, doxorubicin, vincristine, and Peg-Asparaginase, as well as intrathecal methotrexate. Eighteen days after intravenous chemotherapy and 8 days after her seventh intrathecal 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 cytotoxic white matter edema as the underlying mechanism in subacute MTX toxicity. Whether children are more likely to suffer MTX toxicity as a result of different susceptibility or children are simply more commonly treated with intrathecal or high-dose methotrexate requires more investigation. It is particularly important to be aware of this chemotherapeutic side effect in adults, as they are more likely to be misdiagnosed as presenting with an acute cerebral ischemic or hemorrhagic event. The mechanisms of subacute MTX toxicity are poorly understood. Imaging abnormalities obtained in our case suggest a transient cytotoxic white matter edema as the underlying mechanism in subacute methotrexate toxicity.

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 WP-shunt plus RT (group A). Four patients underwent all of EGFR-TKI, RT, and WP-shunt (group B). Mean time to LM onset from diagnosis of lung adenocarcinoma was 24 (8–36) months. Mean 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 peritonic carcinomatosis after WP-shunt. CONCLUSION: Combination of triple modalities (EGFR-TKI, RT, and WP-shunt) is a safe treatment, and may improve outcome of patients with LM from lung adenocarcinoma.

NEUROTOXICITY AND NEUROPROTECTION

P.151*, SUBACUTE NEUROLOGICAL SYNDROME WITH IMAGING CORRELATE FOLLOWING INTRATHecal METHOTREXATE IN AN ADULT

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BACKGROUND: Methotrexate (MTX) is an important chemotherapeutic agent in the management of oncological 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 mimic 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 intrathecal 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 leukemia receiving systemic low-dose MTX, cytarabine, cyclophosphamide, doxorubicin, vincristine, and Peg-Asparaginase, as well as intrathecal methotrexate. Eighteen days after intravenous chemotherapy and 8 days after her seventh intrathecal 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 cytotoxic white matter edema as the underlying mechanism in subacute MTX toxicity. Whether children are more likely to suffer MTX toxicity as a result of different susceptibility or children are simply more commonly treated with intrathecal or high-dose methotrexate requires more investigation. It is particularly important to be aware of this chemotherapeutic side effect in adults, as they are more likely to be misdiagnosed as presenting with an acute cerebral ischemic or hemorrhagic event. The mechanisms of subacute MTX toxicity are poorly understood. Imaging abnormalities obtained in our case suggest a transient cytotoxic white matter edema as the underlying mechanism in subacute methotrexate toxicity.
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 Hu-Dal-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 further exact test were used to compare the frequencies of the different HLA antigens in patients and controls. RESULTS: The frequency of HLA-DQA2 was significantly higher in Hu-PNS patients (33 of 53; 62%) than in HC (881 of 2360; 37%) (P = .000001). Although there also was a trend towards a higher prevalence of HLA-DQB1 in Hu-PNS patients in SCLC patients with Hu-Ab or neurological symptoms and 2440 patients without clinical manifestation of malignancy (6%). However, in patients with other malignancies, it was higher (30%; P = .0072). Odds ratio for the presence of classical NPS in ovarian tumor patients was 1.8. DISCUSSION: 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 5-year survival in Western Poland population.
anti-NMDA antibodies in teratoma patients without neurological deficit. CONCLUSIONS: Classical NPS were found both in patients with neurological deficits preceding clinical diagnosis of malignancy and in cases with other brain tumors causing NPS. Anti-NMDA antibodies can appear in ovarian teratoma patients without neurological deficit. Anti-CV2 antibodies were not found in ovarian tumors patients.

**SUPPORTIVE AND PALLIATIVE CARE**

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

**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 1st of November 2005 to 30th of June 2009. Using a standardised 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 radio/chemotherapy, 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. 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. 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.

**P.157**: INTRAVENOUS AND ORAL LEVETIRACETAM IN PATIENTS WITH A SUSPECTED PRIMARY BRAIN TUMOR AND SYMPTOMATIC EPILEPSY UNDERGOING NEUROSURGERY: THE HELLO STUDY

**BACKGROUND**: Levetiracetam (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 perioperatively 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 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.

**P.158**: INTRACTABLE HEADACHE BECAUSE OF NEOPLASTIC MENSITIS IN TWO PATIENTS WITH GIOBLASTOMA

**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 with 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 radio chemotherapy. 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: Neoplastic Meningitis is a rare complication in malignant glioma patients. Considering the side effects and interactions of other anticonvulsants, LEV seems to be a favorable drug for 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.

**PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA (PCNSL)**

**P.159**: LYMPHOMATOSIS CEREBRI (LC) PRESENTING WITH ORTHOSTATIC HYPOTENSION, ANOREXIA, AND PARAPARESIS

**INTRODUCTION**: Primary central nervous system lymphoma (PCNSL) usually appears to be enhancing mass lesions on neuroimaging. In rare instances, PCNSL occurs as a diffuse infiltrative variant without mass lesion or blood–brain barrier compromise termed LC. In all published cases, LC presented as a rapidly progressive dementia. RESULTS: A 58-year-old woman presented with subacute onset paraparesis, orthostatic hypotension, and 80-pound weight loss. Her symptoms progressed over 6 months and she developed headache. Brain MRI revealed venous sinus thrombosis and nonenhancing foci of FLAIR hyperintensity in pons, corona radiata, subcortical WM, and pons. MRI spine revealed enhancement of lumbar nerve roots. Cerebrospinal fluid suggested malignancy. Cytology was negative despite multiple samples. Bone marrow biopsy, body CT, and body PET were unremarkable. She had subtle radiologic response, but no clinical improvement following steroids. Two months later, she developed encephalopathy, quadraparesis, and progression of the WM lesions. She developed fluctuating hypotension and expired. Systemic autopsy was unremarkable. Gross appearance of the brain and spinal cord was normal, without discrete mass. Microscopic inspection revealed diffuse infiltration of the brain by large B-cell lymphoma. DISCUSSION: Instead of dementia as in all prior published cases, this patient with LC presented with anorexia and orthostatic hypotension. Dementia is usually associated with systemic disease. Diencephalic infiltration is a neurologic cause of anorexia. Entities such as lymphoma, leukemia, or histiocytosis should be considered in patients with weight loss and WM lesions. Rarely, orthostatic hypotension has a CNS cause. Recognition that the brainstem WM lesions...
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 = 0.103). Higher serum level of sIL-2R related to the poor survival (P = 0.015), whereas no significant impacts of serum LDH level and chemotherapy were observed on the prognosis. Multivariate analysis using Cox proportional hazard model showed higher serum levels of sIL-2R was an independent factor for poor survival (P = 0.05). Higher serum level of sIL-2R was strongly associated with a worse 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.

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 value 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 undergoing complete tumor resection in our department between October 2007 and September 2009. All patients had a preoperative KPS of 70 or greater. Surgeries were performed using conventional microsurgical techniques with or without iMRI guidance, employing a mobile 0.15 T device. 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 obtained at 3 T. All patients received adjuvant treatment and were followed on a 3-monthly basis. 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 3 Edinger Institute, Goethe-University, Frankfurt, Germany; 2Department of Neuroradiology, Goethe-University, Frankfurt, Germany; 3Institute of Pathology, University Hospital Heidelberg, Germany

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 35 Gy in 20 fractions to the 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 11–107). Forty patients received 30 Gy to CSI, 5 received 35 Gy, and 2 received <30 Gy. Three had concurrent vincristine only, 3...
had concurrent vincristine and maintenance chemotherapy with CCNU and cisplatin. 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 were 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 5 (3 males, 2 females) have had children post treatment. All relapsing patients were neurologically assessed and deemed to have retained significant neurological function (3 growth hormone, 1 thyroxine, and 1 hydrocortisone). One patient developed epilepsy, 5 hearing impairment, and 2 second malignancies (breast, prostate). None developed meninognoma, thyroid malignancies, or secondary BC. All 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)
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INTRODUCTION: MGMT studies have demonstrated that a limited number of patients with glioblastoma benefit from Temozolamide. 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- c and noncyclical 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 effect of administration of mannitol as a blood–brain barrier disrupter. Measurements were made by Inductively Coupled Plasma Mass Spectrometry (ICP-MS) of 10B concentration in blood, urine, extra-cellular fluid (via brain microdialysis), 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 keeping with 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 irradiation at 1hr after the end of BPA infusion.2 Our study shows delayed peak boron levels in brain and ECP suggesting that the optimal window for delivery of the radiation dose may be approximately 4 hours after infu- sion. Escalation of tumor boron dose without additional dose to normal brain is possible and likely to further facilitate therapeutic response.

REFERENCES

P.165. A COMPARISON OF VOLUMETRIC MODULATED ARC THERAPY (RAPIDARC) AND CONVENTIONAL EXTERNAL BEAM RADIOThERAPY IN TEMPORAL HIGH-GRADE GLIOMAS
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INTRODUCTION: Patients treated for high-grade gliomas in the tem- poral region with external beam radiotherapy are at risk of significant cogni- tive deficits, including short-term memory loss which has a significant impact on daily functioning and quality of life. This is thought to be related to dose received by the hippocampi. Objectives: A feasibility study was done using RapidArc5 (Varian medical systems), a volumetric arc–based intensity-modulated radiotherapy technique (IMRT) to treat high-grade gliomas in the temporal region and to establish if there was a dosimetric advantage of RapidArc compared with conventional radiotherapy with particular refer- ence to dose to the hippocampi. METHODS: Ten patients previously treated with conventional 3D conformal radiotherapy for high-grade gliomas in the temporal lobe region were unplanned using Varian RapidArc. Target volumes, organs at risk (OAR), and dose constraints defined for conventional planning were unchanged, but in addition hippocam- pi, inner ear, and temporal lobes were outlined using MRI fusion. No additional dose constraint was added for hippocampi. Comparisons of doses to the PTv and organs at risk including hippocampi were then made. RESULTS: The conformity 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 more than 1 arc. 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 in 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 because of 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 injury, compared to the conventional approach.}

MISCELLANEOUS

P.166. AWAKE 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 oper- ative 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 per- formed. All patients underwent MRI with neuronavigation 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 years. Nineteen of 47 relapsed (6 outside the radiotherapy treatment fields). Longest interval to relapse was 10 years. Five of 19 patients who relapsed were 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 5 (3 males, 2 females) have had children post treatment. All relapsing patients were neurologically assessed and deemed to have retained significant neurological function (3 growth hormone, 1 thyroxine, and 1 hydrocortisone). One patient developed epilepsy, 5 hearing impairment, and 2 second malignancies (breast, prostate). None developed meninognoma, thyroid malignancies, or secondary BC. All 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.

REFERENCES
P.167. RADIATION-INDUCED OSTEOSARCOMAS AFTER TREATMENT FOR FRONTAL GLIOMAS: A REPORT OF 2 CASES
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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 frontal 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. A 54-Gy radiotherapy was administered. In September 2015, the patient noted an enlarging subcutaneous mass in the right frontal region. CT showed an osteolytic mass in the right frontal sinus. An open biopsy was performed and a histological diagnosis of radiation-induced osteosarcoma was made, but the patient subsequently died of rapid tumor re-growth.

CASE 2: A 58-year-old male underwent partial resection of a bifrontal tumor in May 1996. The histological diagnosis was anaplastic oligoastrocytoma. Radiotherapy of 36 Gy was administered. The patient was subsequently readmitted in March 2008 because of a marked deterioration in general health. As tumor recurrence was suspected in the left frontal lobe and a 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.

P.168. CEREBRAL VENOUS SINUS THROMBOSIS IN A PATIENT WITH METASTATIC GERM CELL TUMOR
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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 sclerotum nodes and bone (L3, direct extension from retroperitoneal mass) was admitted for initial chemotherapy (CT). A week after the completed first cycle of CT according to BEP (bleomycin, etoposide, cisplatin), he returned to the inpatient ward with new seizures progressing to epileptic status and left-sided hemiparesis. On 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 retrospectively 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 FLAIR, 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 transverse and partial thrombosis of the sagittal sinus with ischemic 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 CT. After complete regression of mediastinal and sclerotic masses, the residual retroperitoneal mass was excised. No vital malignant cells were found. He received postoperative irradiation (L3) and is in complete remission for more than half a year. CONCLUSION: The complication of CVST in the presented patient was probably related to cancer and CT, which had been performed long after initial symptoms. Further studies are necessary to clarify the natural history of CVST in cancer patients. This case demonstrated that CVST can be a rare complication, adequately diagnosed by MRI and MR venography (MRV) with high sensitivity and specificity, in an oncology patient with brain metastases.

P.169. THE USE OF COMPLEMENTARY AND ALTERNATIVE MEDICINES (CAM) IN BRAIN TUMOR PATIENTS
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INTRODUCTION: Complementary and alternative medicines (CAM) are known to be used by cancer patients, but little is known about the use of CAM by brain tumor patients. We conducted a survey to determine the frequency of CAM use and its correlation with demographic and clinical factors. METHODS: Questionnaires were distributed to patients in neuro-oncology outpatient clinics, the radiotherapy department, and the chemotherapy suite. Patients were asked to fill out the questionnaire anonymously and return it in a prepaid envelope. The questionnaire included demographic information and diagnostic categories. Patients were asked to record the use of CAM by selecting treatments from a predefined list and give information about how they accessed and funded this. RESULTS: Thirty-three questionnaires were analyzed. Diagnoses included meningioma, high- and low-grade glioma, germinoma, and posterior PNET. Fifty-five percent of patients questioned the use of CAM. There was almost no gender difference with a higher than previously reported use in men. The majority of patients (79%) were in the younger age group (21–40 years). In addition, there was a positive correlation between the use of CAM and having more than one cancer diagnosis. Sixty-four percent of patients reported the use of CAM during treatment with either radiotherapy or chemotherapy. Only 22% of patients disclosed CAM use to the treating oncologist. Most patients learnt about CAM from family and friends, and funded themselves for treatments. There were differences in professional use of CAM between the two centers. Importantly, the patients who had used CAM had a better quality of life, were willing to take a higher risk, and were less satisfied with conventional medical care. CONCLUSION: CAM use is common in brain tumor patients. Many patients used CAM without disclosing this information to their treating oncologists. Further studies are necessary to clarify the indications, contraindications, and possible interactions between some CAM and radiotherapy and chemotherapy. This highlights the need to specifically question brain tumor patients about CAM use and to be able to advise patients on potential interactions.

P.170. THE ROLE OF A SPECIALIST THERAPEUTIC RADIOGRAPHER WITHIN THE MULTI-PROFESSIONAL NEURO-ONCOLOGY TEAM
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The role of 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 with a radio-therapeutic background are also essential in managing the complex neuro-oncology patient. The CNS is adept at selecting treatments from a predefined list and give information about 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 would be highly useful among cancer patients, but there is very little evidence for the effectiveness of a Radiographer within a neuro-oncology team. The fundamental goal of the team is to ensure that patients across the entire treatment pathway benefit from the expertise of the Radiographer. This paper will discuss the set-up and development of a new role of the Radiographer within the multidisciplinary neuro-oncology team with specific reference to Radiotherapy. This role will be based on the patient-centred model of care, which aims to improve patient care and overall well-being. The Radiographer is responsible for delivering a training package for radiographers in order to improve the delivery of care. The role of the Radiographer within the neuro-oncology team will be discussed, with a focus on the impact on patient care and outcomes. The Radiographer will be responsible for delivering a training package for radiographers in order to improve the delivery of care. The role of the Radiographer within the neuro-oncology team will be discussed, with a focus on the impact on patient care and outcomes. The Radiographer will be responsible for delivering a training package for radiographers in order to improve the delivery of care.
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 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 15 females, with a median age of 33 years (range 19.9–82.3). In 31 cases, there was a known family history for only one-third of patients. RESULTS: The number of treated lesions in one procedure was 3.9 (1–18), with a mean number of 1.6. Seventy-eight percent of patients have a complete control group, 3 patients had their lesions previously embolized, and 2 had received fractionated radiotherapy while in the nonsurgical group, 5 patients had received endovascular treatment, and 1 had fractionated radiotherapy. At the time of treatment, 6% of the operated cases were asymptomatic, and 81% and 94% had low cranial nerve and VII 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 VII, 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 15.53 cm³ (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 50,000 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 January 2008 and June 2009, 70 treatments in 33 NF2 patients have been performed. 12 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). Fourteen 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 19.4 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 meninges and 62 schwannomas were treated. In 35 cases, the 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. Neuroradiological follow-up, and performing informed consent. Objectives include forging closer ties with the physics department to develop stereotactic IMRT, and supine craniospinal therapy delivery.

**P.173. EXPLORING A NEW THERAPY FOR NEUROBLASTOMA:**
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**Neuroblastoma** is one of the most common childhood cancers. Malignant neuroectodermal tumors 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 double-cortin-like kinase (DCLK) gene transcripts are crucial markers for correct protein expression 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 normal or malignant cells. Suppression of DCLK by short-interfering RNA (siRNA) disrupted the motility 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 one of 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-siRNA 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, chemotheraphy, anti-epileptic drugs, steroids, and anxiety and depression are commonly described factors. However, the prevalence of CD is difficult to estimate. Discrepancies among studies are frequently explained by methodological differences. Performance status scales (KPS, ECOG) and short screening tests (MMSE, MDRS) have a low sensitivity 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 (3), grade I (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-OSEOUS PSEUDOTUMOR: THE ROLE OF SURGICAL EXCISION J. F. Megyesi, F. Haji, M. Alturkustani, A. Parrent, I. Gulka, and R. Hammond; University of Western Ontario, London, ON, Canada

BACKGROUND: Fibro-osseous lesions are a rare clinical entity. We present the case of a 65-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 therapy 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 pathophysicsology 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 gliosis 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 T. Jiang1, Y. Lin2, X. Zhang3, X. Zhu4, X. Peng4, J. Yang5, H. Huang6, G. Tang7, X. Chen7, H. Xing7, X. Su8, and W. Zhang1;1Beijing Tiantan Hospital, Capital Medical University, Beijing, China; 23rd Section, Beijing Hospital, Puyang City, China; 3Center of Disease Control of Shanghai Baoshan district, Shanghai, China; 4Neurosurgical Department of Daqing Longnan Hospital, Daqing City, China; 5Neurosurgical Department of Pu-ya Oilfield General Hospital, Pu-ya City, China; 6Health Administration of China, Beijing, China

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-yang 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.

P.177. POTENTIATING EFFECTS OF PARP INHIBITION ON CHEMO- AND RADIOTHERAPY TREATMENT IN SERUM-FREE GILOMA CELLS R. K. Balvers1, J. J. Kloezen1, J. K. H. Spoore1, C. M. F. Dirven1, M. L. M. Lamfers1, and S. L. Lamfers1;1Dept. of Neurosurgery, Erasmus MC Rotterdam, Rotterdam, Netherlands; 2Department of Neurosurgery, St. Elizabeth Ziekenhuis, Tilburg, Netherlands

INTRODUCTION: The dismal prognosis of patients diagnosed with glioblastoma multiforme (GBM) urges researchers to investigate new treatment modalities for targeted drug regimens. Recent reports on glioma tissue cultured under serum-free (SF) conditions show that glioma stem cells (GSC) are preferentially selected, and that these cultures preserve a good resemblance to the original tumor on DNA and RNA level. Several publications have illustrated GSC’s to be more resistant to chemotherapeutic agents and radiation therapy. This led us to develop a high throughput model for screening promising combination therapies. By isolating GSC’s from freshly isolated high-grade glioma (HGG) samples, we were able to test the effect of poly(ADP-ribose) (PARP) inhibitor ABT-888 in combination with temozolomide (TMZ) and radiotherapy (RT). METHODS: Freshly isolated HGG samples were cultured under SF conditions as neurospheres. SNP analysis of both low (p1–p4) and higher passages (p5–p11) illustrated the genetic stability and resemblance to the parental tumor tissue. The samples that were successfully expanded were tested in several cytotoxicity studies. Cells were seeded in monolayer on 96-well plates coated with extracellular matrix. Treatment consisted of 0.1 and 0.01 μM TMZ and 1 and 0.5 GY RT. The combined effect with ABT-888 was tested with aforementioned dosing of TMZ or RT, combined with 2.5 or 10 μM of ABT-888. Read out of therapeutic effect was assessed on day 5 and 8 by performing the Cell Titer GLO assay (Promega) in triplicate. We validated the data by parallel testing of TMZ resistant (T98) and sensitive (U373) glioma cell lines. MGMT expression was investigated by Western blotting (WB) of the cell cultures. RESULTS: We tested 9 SF cultured primary GSC cultures for TMZ or RT and ABT-888 combination therapy. Of these samples, the clinical histological diagnosis was: GBM (n = 6) and anaplastic OD (n = 3). ABT-888 did not sort out any effect as a single agent. TMZ resistance at 100 μM dosing was found in 7 out of 9 cell cultures (<25% decrease in viability). Of these samples, we found a potentiating effect (25–75% decrease in viability) of ABT-888 addition in 6 cultures at a 2.5 μM ABT-888 (n = 1) or 10 μM ABT-888 (n = 5). We observed no detectable MGMT expression in TMZ sensitive cultures on WB. TMZ-resistant cultures expressed MGMT in 4 of 7 cases. ABT-888 reversal of TMZ resistance appeared in both MGMT-positive as well as negative cultures. For RT, we found resistance at 6 Gy in 2 out of 9 cell cultures. Both cell cultures did not show any potentiating effect of ABT-888. CONCLUSIONS: We were able to culture and expand GSC’s from HGG samples. These cultures were found to genetically resemble the parental tumor tissue. We found that TMZ-resistant cultures could be sensitized by adding ABT-888 to the medium. The RT resistance could not be reversed. On the basis of these findings we are further elucidating the synergy of alkylating agents in combination of PARP inhibitors.
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 were analyzed. In total, 1147 miRNA were detected and analyzed. 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.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 unsolicited, 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 a 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.