ORAL PRESENTATIONS

NEURO-IMAGING I

O.01. INFLUENCE OF P-GLYCOPROTEIN EXPRESSION ON 99M-TC-TETROFOSMIN UPTAKE IN GLIOMAS
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OBJECTIVE: Multidrug resistance (MDR) remains a major obstacle to successful chemotherapeutic treatment of cancer and can be caused by overexpression of P-glycoprotein, the MDR1 gene product. P-glycoprotein (P-gp) recognizes several chemotherapeutic agents as a substrate and prevents their accumulation. Among them, both technetium-99-sestamibi and technetium-99-tetrofosmin (99mTc-TF) are single photon emission computed tomography tracers. 99mTc-MIBI uptake has been proven in vitro and in vivo to inversely correlate with P-gp levels of tumors. In vitro studies have shown that 99mTc-TF is influenced in a lesser degree from the P-gp expression, thus may be superior to 99mTc-MIBI for brain tumor imaging. In the present study, we evaluated in vivo whether 99mTc-TF uptake correlates with P-gp levels in gliomas.

MATERIALS AND METHODS: Eighteen patients (10 males, 8 females, mean age 57.3 years) with histologically confirmed glioma were included in the study. There were 13 glioblastoma multiforme cases, 2 anaplastic astrocytomas, 2 anaplastic oligodendrogliomas, and 1 low grade astrocytoma. Brain SPECT by 99mTc-TF was performed within a week prior to surgical excision and the expression of P-gp was assessed by immunohistochemistry. Radiotracer accumulation was assessed by a semiquantitative method of image analysis, calculating the lesion-to-normal (L/N) uptake ratio. RESULTS: The tracer uptake ranged from faint to profound (mean L/N = 82.5, range 1.8–20). The P-gp expression ranged from 0% to 45%. Using Spearman’s rho analysis we found no correlation between tracer uptake (L/N) and P-gp expression (rho = 0.538). CONCLUSION: The present data suggest that 99mTc-TF uptake is not influenced by P-gp expression in gliomas. Thus, 99mTc-TF constitute a suitable radiotracer for gliomas imaging.

O.02. PERFUSION MR IN DIFFERENTIATING BETWEEN TUMOR-PROGRESSION AND PSEUDO-PROGRESSION IN RECURRENT GLIOBLASTOMA MULTIFORME
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OBJECTIVES: The aim of this study was to evaluate perfusion magnetic resonance imaging (pMRI) for differentiation of tumor progression (PD) from pseudo-progression (Ps-PD) in patients with recurrent glioblastoma multiforme (GBM) following chemoradiation. BACKGROUND: The appearance of Ps-PD on brain MR following initial chemoradiation is difficult to distinguish from true PD. We examined whether the technique of pMRI allows proper distinction between PD and Ps-PD in patients with recurrent GBM. METHODS: All files of patients with GBM with a history of recurrent disease were assessed, local (unifocal disease), distant (second lesion nonconcurrent, at first, second, and third recurrence. Four patterns of radiographic progression 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 surgery followed by bevacizumab and a cytotoxic chemotherapy, cytotoxic chemotherapy alone, or on an investigational trial. Magnetic resonance imaging (MRI) and diffusion-weighted imaging were analyzed at four points in time in each patient: at presentation, at first, second, and third recurrence. Four patterns of radiographic disease were assessed, local (unifocal disease), distant (second lesion nonconiguous with primary lesion), multifocal (>2 lesions including leptomeningeal dissemination), and diffuse. RESULTS: At presentation, 87.5% of glialomas were local, 6.25% distant, 3.75% multifocal, and 2.5% diffuse. At first recurrence following progression on RT/TMZ and before initiation of bevacizumab, 80% were local, 7.5% distant, 6.25% multifocal (including 1 with CSF dissemination), and 6.25% diffuse. At second recurrence following progression on bevacizumab, 71.25% were local, 8.75% distant, 8.75% multifocal (2 of 7 with CSF dissemination), 11.25% were diffuse. At third recurrence (57 patients evaluable), 71.25% were local, 7.0% distant, 7.0% multifocal, and 14.0% were diffuse. Survival following progression on bevacizumab did not differ by pattern of radiographic recurrence. CONCLUSION: A majority of adult patients with GBM at diagnosis manifest MRI-defined local disease and maintain this pattern notwithstanding multiple recurrences and treatment with bevacizumab.
O.05. PREOPERATIVE ESTIMATION OF EXTENT OF RESSECTION ON GLIOMAS BY DTI-FIBER TRACKING

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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 (SLF) fasciculi 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 functional boundaries. 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 tumor showed more than one tract infiltration. Tract infiltration depended on 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 each involved tracts (mainly CST, IFO, and SLF) allowed anticipating 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: [11C]-L-[Methyl-14C]methionine (MET) positron emission tomography (PET), [18F]-fluoro-2-deoxy-2-[18F]fluorohydrindine (FLT) PET, and [18F]-fluoromisonidazole (FMISO) are sensitive modalities for visualizing proliferating tumor and brain normal tissue. The objectives of this study were to analyze the relationships between the uptake of MET, FLT, or FMISO and the histopathological grading in gliomas. MET-PET: We examined 51 patients (22 males, 29 females; mean age: 48.7 years; range: 2–89 years; 12 diffuse astrocytomas, 1 oligodendroglioma, 16 anaplastic oligodendrogliaoma, 6 anaplastic ependymomas, and 19 glioblastomas). FLT-PET: A total of 220 patients with gliomas (mostly low grade) were included. In all patients, the cortico-spinal tract (CST), the inferior fronto-occipital (IFO), and superior longitudinal fasciculus (SLF) were reconstructed by DTI-FT. FLT SUVmax in the tumor had a stronger correlation with Ki-67 index than MET SUVmax. CONCLUSIONS: PET studies using MET-PET, FLT-PET, and FMISO are useful for preoperative diagnosis in gliomas. FLTPET seems to be superior to MET-PET in assessment of the proliferation activity on gliomas of different grades. FMISO-PET is useful for non-invasive assessment of hypoxia in malignant gliomas. Advances in molecular imaging such as PET imaging techniques will facilitate more safe and solid management and therapy for the patients with malignant gliomas.

0.07. MGMT PROMOTER METHYLATION STATUS AND EXPRESSION OF DNA MISMATCH REPAIR GENES IN PAIRED PRIMARY AND RECURRENT GLOBLASTOMA: A TRANSLATIONAL 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 hereby addressed the question whether GBM relapses are associated with changes in the MGMT promoter methylation status or altered expression of the DNA mismatch repair genes MLH1, MSH2, MSH6, or/and PMS2. METHODS: MGMT promoter methylation status was assessed in paired primary and recurrent glioblastomas of 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: 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 in 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, immunohistochromical 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 changes, as protein levels were not significantly reduced in the recurrent tumor when compared with the corresponding primary tumor. Accordingly, the changes in the MGMT promoter methylation status are unlikely to account for acquired resistance to temozolomide.

0.08. MGMT mRNA TRANSCRIPTIONAL ACTIVITY PREDICTS CLINICAL OUTCOME IN MALIGNANT GLIOMAS AFTER RADIOTHERAPY/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 radiotherapy/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). CONCLUSIONS: In this prospective, randomized, open-label, phase III trial, both tumors that reduce MRI enhancement by restoring the blood-brain barrier, local therapies, posttreatment changes that may mimic tumor, and lack of defining tumor resection margin as positive. Therefore, a RR of 250% (15%) is not significantly different from 0.0% in the primary analysis. A RR of 250% (15%) was observed in the population of glioblastoma patients. These results are consistent with the hypothesis that TTFields may inhibit growth of secondary tumors that form after surgical resection or biopsy of the primary glioblastoma. 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 Bent1,2, D. MacDonald,3 S. Chang,4 M. A. Vogelbaum,5 and P. Y. Wen6 1Memorial Sloan Kettering Cancer, New York, NY; 2London Regional Cancer Center, London, ON, Canada; 3UCSF, San Francisco, CA; 4Cleveland Clinic, Cleveland, OH; 5Dana Farber and Brigham’s and Women’s 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. 1990; 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 ability 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 a ongoing unoffical 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; 28:1277); based on measuring cross-sectional enhancing tumor area, taking into account changes in steroid dose and neurological status (Wen et al. J Clin Oncol. 2010; 28:1277). 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-angiogenetic agents. Hindsgaul 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. O.10. A PROSPECTIVE, RANDOMIZED, OPEN LABEL, PHASE III CLINICAL TRIAL OF NOVOTTF-100A VS BEST STANDARD OF CARE CHEMOTHERAPY IN PATIENTS WITH RECURRENT GLIOBLASTOMA R. Stupp1, A. Kammer2, H. Engelhard3, V. Heidecke4, S. Taillibert5, F. Lieberman4, V. Dhabay6, E. D. Kirson7, Y. Palti8, and P. H. Gutin9 1University Hospital (CHUV) and University of Lausanne, Lausanne, Switzerland; 2TASMC, Tel Aviv, Israel; 3University of Illinois Chicago (UIC), Chicago, IL; 4Klinikum Augsburg, Augsburg, Germany; 5Hôpital Pitie-Salpetriere, Paris, France; 6University of Pittsburgh Medical Center (UPMC), Pittsburgh, PA; 7Na Homolce Hospital, Prague, Czech Republic; 8NovoCare Ltd., Haifa, Israel; 9Memorial Sloan Kettering Cancer Center (MSKCC), New York, NY BACKGROUND: The NovoTTF-100A device is a portable, home use, medical device which delivers low intensity, intermediate frequency, alternating electric fields (TTF fields) to the brain by means of non-invasive, disposable scalp electrodes. TTF fields physically interfere with cell division and assembly of organelles (Kirson et al. Cancer. 2004; 2004: Kirson et al. Proc Natl Assoc Sci USA, 2007; Salzberg et al. Oncology, 2008; Kirson et al. BMC Med. Phys. 2009). METHODS: Adult patients with recurrent GBM were randomized (1:1) to either NovoTTF-100A administered continuously (20–24 hours/day, 7 day/week) or the best local standard of care (BSC) chemotherapies, at the physicians discretion, in each center. Randomization was stratified by prior surgery for recurrence and center. The number of prior treatments was not limited; a Karnofsky performance status of ≥70% and an adequate end-organ function were required. The primary endpoint was overall survival; secondary endpoints included 1-y survival, PFS6, TTP, radiological response rate and safety. The study was powered to detect a 60% increase in overall survival (eg, 45 vs 30 weeks) with a two-tailed α = 0.05 and power of 0.80. RESULTS: Between September 2006 and May 2009, 237 patients were included in 28 centers in the United States, Europe, and Israel, 120 patients were treated withNovoTTF-100A alone, and 117 patients received BSC chemotherapies including bevacizumab, nitrosureas, procarbazine, or PCV combination. Thirty-two tumors were to be randomized (1:1) to either NovoTTF-100A administered continuously (20–24 hours/day, 7 day/week) or the best local standard of care (BSC) chemotherapies, at the physicians discretion, in each center. Randomization was stratified by prior surgery for recurrence and center. The number of prior treatments was not limited; a Karnofsky performance status of ≥70% and an adequate end-organ function were required. The primary endpoint was overall survival; secondary endpoints included 1-y survival, PFS6, TTP, radiological response rate and safety. The study was powered to detect a 60% increase in overall survival (eg, 45 vs 30 weeks) with a two-tailed α = 0.05 and power of 0.80. RESULTS: Between September 2006 and May 2009, 237 patients were included in 28 centers in the United States, Europe, and Israel, 120 patients were treated withNovoTTF-100A alone, and 117 patients received BSC chemotherapies including bevacizumab, nitrosureas, procarbazine, or PCV combination. RESULTS: Between September 2006 and May 2009, 237 patients were included in 28 centers in the United States, Europe, and Israel, 120 patients were treated withNovoTTF-100A alone, and 117 patients received BSC chemotherapies including bevacizumab, nitrosureas, procarbazine, or PCV combination. 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O.12. EFFICIENT ENGRAFTMENT OF MGMTP140K GENE-MODIFIED CD34+ CELLS FOLLOWING NONMYELOABLATIVE BCNU CONDITIONING IN PATIENTS WITH MALIGNANT GLIOMA

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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-β-phenylguanine (O6BG) has been used, but has been associated with dose-limiting hematopoietic toxicity. 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 chemoprotection 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 (427 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 days and nadir thrombocytopenia 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 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 2.12 cycles of 60BG/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 hematopoietic toxicity has been observed. Up till now, the feasibility of achieving significant engraftment of MGMTP140K-modified cells with a well-tolerated dose of BCNU. Follow-up further will determine whether this approach will allow for further dose escalation of TMZ and improved survival.

MOLECULAR MARKERS I

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

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Up till now, typing and grading of diffuse gliomas is based on histopathological features. However, because of, especially, lack of unequivocal criteria and sampling, the robustness of this classification is suboptimal, and more objective tools are needed for more reliable assessment of their biological behavior (eg, nearly all low-grade diffuse gliomas eventually progress to high-grade malignancy); however, time to progression varies considerably and there is currently no valid parameter that unambiguously predicts how rapidly malignant progression will occur. Over the last decades it has become increasingly clear that molecular genetic markers are helpful in recognizing more uniform subgroups of gliomas (eg, loss of chromosome 1p and 19q is reported to predict longer survival and better response to (chemo)therapy whereas methylation of the MGMT gene predicts chemosensitivity to alkylating agents). Furthermore, several genes were reported to be involved in malignant progression of gliomas; however, detailed information about their “timing” and cooccurrence in the course of molecular progression is relatively lacking. We therefore evaluated in a spectrum of over 300 diffuse gliomas the (co-)occurrence of copy number changes involving chromosomes 1p and 19q, CDKN2A, PTEN, and EGFR(VIII) as detected by Multiplex Ligation-dependent Probe Amplification (MLPA). Our results show that high malignancy grade is associated with particular copy number changes and the cooccurrence of these changes. Consequentially, also in cases that are histopathologically still diagnosed as a low-grade glioma, such changes may indicate aggressive tumor behavior. Based on our findings we propose a scheme for the timing of the different events in the course of molecular progression, molecular malignancy being characterized by the cooccurrence of multiple changes and their exact malignant character (hem-1 homozygous loss; low-level gain (high-copy) amplification). Interestingly, different types of 1p/19q aberrations were identified, some of them being indicative for molecular malignancy (partial or isolated 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, PYRSEQUENCING, AND IMMUNOHISTOCHEMISTRY FOR MGMT ANALYSIS

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MGMG status is a predictive factor of response to standard treatment of newly diagnosed glioblastomas involving temozolomide (TMZ) and radiotherapy and is used as a prognostic factor (median survival of 12 months) notwithstanding aggressive treatment. Combination chemotherapy of TMZ and radiotherapy is 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 (centralized MS-PCR, gene marking in white blood cells) the reproducibility of MGMT methylation assays, 3 primary cell lines (GB2 and GB3), were tested in 10 separate series. GB2 and GB3 were never methylated (Meth) with either MethLight or MS-HRM, but were Meth in 7 of 10 and 9 of 10 cases with MS-PCR, respectively, while mean methylation levels were 5% and 9% for PRY, with reproducibilities of 11% and 6%, respectively. GB2 was always Meth with MS-HRM and MS-PCR, methylation levels being 42% and 77% for MethLight and PRY, with reproducibilities of 72% and 7%, 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 cases were immunostained and analyzed in 4 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. Following tests on 99 samples from patients with newly diagnosed GBM treated with standard treatment (radiation and TMZ), the best predictive values for overall survival were obtained by PRY (P < .0001 cut off 9%), MS-PCR (P < .0001), and IHC (P < .001 cut off 25%). MethLight (P = 0.09) and MS-HRM (P = 0.03) yielded disappointing results in this series of patients. Contrary to recent studies, MGMT expression assessed by IHC was well correlated with overall survival. As observer variability is a reported problem with this technique, which could account for the poor reproducibility observed in this study, stained slides are currently evaluated by 2 other pathologists to validate the result. For MGMT promoter methylation analysis, PYR appears to be a very robust technique and a good alternative to classical MS-PCR, which is not well adapted to clinical practice. The next step of the project aims at implementing these techniques in different laboratories.

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

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BACKGROUND: The NDRG2 gene is a member of the N-myc downstream-regulated gene family that is located on chromosome 14q11.2. It has been proposed that the NDRG2 gene is a candidate tumor suppressor gene (TSG), which the expression of the protein encoded by this gene is only observed in selected gliomas and promotes cell differentiation. Consistent with its potential function as a TSG, downregulation
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, MATERIALS AND METHODS: The human glioma tumor samples consisted of 19 GBs (WHO grade IV) and 59 oligodendrogial tumors (OTs), 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 reaction (PCR) analysis. 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 92.3% (12 of 13) of GBs. In contrast, only 7.1% (1 of 14) 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 hypermethylation of NDRG2 and high-grade OTs (p = 0.459; P < .01). CONCLUSION: Taken together, our results suggest inactivation 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
M. Aubry 12, M. de Tayrac 1, S. Saï kali 2, A. Etcheverry 1, A. Hamlat 2, CLINICAL OUTCOME IN HIGH-GRADE GLIOMAS
O.16. A FOUR-GENE SIGNATURE ASSOCIATED WITH CLINICAL OUTCOME IN HIGH-GRADE GLIOMAS
M. Aubry 12, M. de Tayrac 1, S. Saï kali 2, A. Etcheverry 1, A. Hamlat 2, T. Lesimple 1, V. Quillien 12, P. Menet 1, and J. Mosser 12, 1CNRS UMR 6061, Rennes, France; 2University Hospital, Rennes, France; 3CRLCC, Rennes, France; 4University Hospital, Angers, France

Molecular studies of high-grade gliomas (HGGs) have highlighted the heterogeneity of these tumors, and have linked molecular signatures to the clinical behavior of tumors expressing such signatures. The ability to identify such molecular subtypes of tumors is essential for guiding therapeutic advances. We report the development and validation of a robust four-gene signature for 176 patients with complete data for all variables and for a patient subgroup. Lack of hTERT expression in the tumor tissue is associated with tumor aggressiveness. These biomarkers were used to confirm that both the mutations of IDH1 or the promoter hypermethylation was associated with survival benefit (p < .01 in the whole cohort and P < .05 in the subset). Additionally, the ability to identify such molecular subtypes of tumors is essential for guiding therapeutic advances. We report the development and validation of a robust four-gene signature associated with outcome. We identified 831 patient subgroup. Lack of hTERT expression in the tumor tissue is associated with tumor aggressiveness. These biomarkers were used to confirm that both the mutations of IDH1 or the promoter hypermethylation was associated with survival benefit (p < .01 in the whole cohort and P < .05 in the subset). Additionally, the ability to identify such molecular subtypes of tumors is essential for guiding therapeutic advances. We report the development and validation of a robust four-gene signature associated with outcome.

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-cellular epochs. Tumors expressed hTERT with a focus on glioblastomas (GBMs) and to investigate its relation 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 (n = 96) by RT-PCR and calculated relatively to GAPDH mRNA. Data were verified in sub-sets 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 GBMs (79 of 272) displayed hTERT gene expression. Out of these the vast majority (87%) of non-tumoral brain tissue were detected in 50% (5 of 10) of high grade OTs, and 92.3% (12 of 13) of GBs. In contrast, only 7.1% (1 of 14) 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 hypermethylation of NDRG2 and high-grade OTs (p = 0.459; P < .01). CONCLUSION: Taken together, our results suggest inactivation 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.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 IDH2 activity and the acquisition of an alpha-ketoglutarate reductase activity. Using direct sequencing and new PCR approaches such as COLD PCR (comapilication at lower denaturation temperature—PCR) combined with high-resolution melting (HRM), we investigated the mutational status of IDH1 and IDH2 genes in 2272 human brain cancers. The aim of the study was to identify the importance of isoform IDH2.

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-cellular epochs. Tumors expressed hTERT with a focus on glioblastomas (GBMs) and to investigate its relation 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 (n = 96) by RT-PCR and calculated relatively to GAPDH mRNA. Data were verified in sub-sets 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 GBMs (79 of 272) displayed hTERT gene expression. Out of these the vast majority (87%) of non-tumoral brain tissue were detected in 50% (5 of 10) of high grade OTs, and 92.3% (12 of 13) of GBs. In contrast, only 7.1% (1 of 14) 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 hypermethylation of NDRG2 and high-grade OTs (p = 0.459; P < .01). CONCLUSION: Taken together, our results suggest inactivation 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.
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 appropriate 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. PATIENTS AND METHODS: The enrollment 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 stage ≥ 2, glucose level in CSF ≥ 2.7 mmol/L, and presence of infratentorial symptoms. Each variable is scored as 0 or 1, according to the absence or presence. Group of unfavorable PI includes patients who score ≥ 2 points. The impact of single parameters on overall survival is determined by both univariate and multivariate analysis. RESULTS: Up to now, 73 patients are enrolled. Data from the first 46 patients included with complete follow-up was analyzed. Thirty-four patients received intrathecal with or without systemic chemotherapy. Univariate analysis identified female sex, breast cancer, Karnofsky Performance Status, negative CSF cytology, PI, and treatment (intra/leural with or without systemic chemotherapy) as a prognostic influence on survival. However, multivariate analysis revealed that breast cancer (HR: 3.03; 95% CI: 1.22–7.46, P = .012), treatment (HR: 2.77; 95% CI: 1.18–7.69, P = .021), negative CSF cytology (HR: 3.85; 95% CI: 1.33–11.11, P = .012), and treatment (HR: 7.14; 95% CI: 2.5–20, P < .001), and PI (HR: 2.77; 95% CI: 1.11–7.14, P = .001) 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, nonneoplastic 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.

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 the use of stereotactic radiosurgery 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 linear-based stereotactic radiosurgery (SRS) system. METHODS: We retrospectively evaluated 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 (Excactr 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 12–21.1 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 to 5 patients (3 received WBRT, 1 received further radiosurgery, and 1 received systemic therapy only). No grade 3 or higher toxicity was recorded. Factors associated with lack of CNS failure (local or distant) included a single brain metastasis and long interval between initial cancer diagnosis and the development of brain metastasis. The frameless image-guided radiosurgery was delivered with submillimeter accuracy. The minimal residual setup error was 0.45 mm (SD = 0.19 mm) and the mean intrafraction motion was 0.37 mm (SD = 0.31 mm). CONCLUSIONS: Image-guided frameless stereotactic radiosurgery to the resection cavity following 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 MULTICENTER PHASE II TRIAL OF THE SWISS GROUP OF CLINICAL CANCER RESEARCH (SAKK) #70/03

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BACKGROUND: Patients with BM rarely survive >6 months and are commonly excluded from clinical trials. We aimed at improving outcomes by exploring 2 combined modality regimens with at the time novel agents for which single-agent activity had been shown. METHODS: NSCLC patients with multiple BM were randomized to WBRT (10 × 3 Gy) and either GFT 250 mg p.o. daily or TMZ 75 mg/m² p.o. daily × 21/28 days, starting on Day 1 of RT and to be continued until PD. Primary endpoint was overall survival, a Simon’s optimal 2-stage design was based on assumptions for the 3-month survival rate. Cognitive functioning and quality of life were also evaluated. RESULTS: Fifty-nine patients (36 M, 23 F; 9 after prior chemo) were included. Median age was 61 years (range 46–82), WHO PS was 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. A arm was closed early after stage 1 analysis when the prespecified 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% (intensive perfusion (2 patients), pneumonia (2), pulmonary embol (1), pneumonia NOS (1), seizure (1)). We summarize here other patients’ characteristics for the 2 trial arms: TMZ (n = 43)/GFT (n = 16); median treatment duration: 1.6 /1.8 mo; Grade 3–4 toxicity: lymphopenia 5 patients (12%) (fatigue 8 patients (19%) 2 patients (13%)), Survival data for TMZ/GFT arms, 3-month survival rate: 58% (95% CI 42.1–73%) 62.5% (95% CI 35–85%); median OS: 4.9 months (95% CI 2.5–5.6)/6.3 months (95% CI 2.2–14.6); median PFS: 1.8 months (95% CI 1.3–1.8)/1.8 (95% CI 1.1–3.9); median time to neuro. progr.: 8.0 months (95% CI 2.2–X)/4.8 (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 functioning failed to show significant improvement. Indications and patient selection for palliative treatment should be revisited and careful monitoring and supportive care is required. Research and progress for this frequent clinical situation is urgently needed.

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

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BACKGROUND: Patients with BM rarely survive >6 months and are commonly excluded from clinical trials. We aimed at improving outcomes by exploring 2 combined modality regimens with at the time novel agents for which single-agent activity had been shown. METHODS: NSCLC patients with multiple BM were randomized to WBRT (10 × 3 Gy) and either GFT 250 mg p.o. daily or TMZ 75 mg/m² p.o. daily × 21/28 days, starting on Day 1 of RT and to be continued until PD. Primary endpoint was overall survival, a Simon’s optimal 2-stage design was based on assumptions for the 3-month survival rate. Cognitive functioning and quality of life were also evaluated. RESULTS: Fifty-nine patients (36 M, 23 F; 9 after prior chemo) were included. Median age was 61 years (range 46–82), WHO PS was 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. A arm was closed early after stage 1 analysis when the prespecified 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% (intensive perfusion (2 patients), pneumonia (2), pulmonary embol (1), pneumonia NOS (1), seizure (1)). We summarize here other patients’ characteristics for the 2 trial arms: TMZ (n = 43)/GFT (n = 16); median treatment duration: 1.6 /1.8 mo; Grade 3–4 toxicity: lymphopenia 5 patients (12%) (fatigue 8 patients (19%) 2 patients (13%)), Survival data for TMZ/GFT arms, 3-month survival rate: 58% (95% CI 42.1–73%) 62.5% (95% CI 35–85%); median OS: 4.9 months (95% CI 2.5–5.6)/6.3 months (95% CI 2.2–14.6); median PFS: 1.8 months (95% CI 1.3–1.8)/1.8 (95% CI 1.1–3.9); median time to neuro. progr.: 8.0 months (95% CI 2.2–X)/4.8 (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 functioning 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.
conflicting results for brain tumors. Moreover, their role for brain tumor invasion is not defined. We therefore aimed to investigate the kinetics of recruitment, the spatiotemporal interaction with tumor vessels and tumor cells, and the migratory pattern of intravenously applied cells from the bone marrow of β-actin eGFP transgenic mice: (a) lineage depleted hematopoietic precursor cells (lineage negative = CD5 −, CD11b −, CD19 −, CD45R −, Ly-6G −, TER119 −; (b) hematopoietic stem cells (lin −, Sca-1 +, c-Kit +, and NG2−); and (c) mature macrophages (lin +, CD11b +). To achieve this aim, multiphoton laser scanning microscopy (MPLSM) in combination with a chronic cranial window was used to image both red-fluorescent U87 glioma cells and eGFP-expressing cell populations (a–c) within the glioma micromilieu. Blood vessels were highlighted by yellow fluorescence.

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

O.26. NOTCH PATHWAY BLOCKADE AFFECTS THE MIGRATORY AND DIFFERENTIATING CAPACITY OF BRAIN TUMOR INITIATING CELLS
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BACKGROUND: The high-grade glioma, glioblastoma multiforme (GBM) is the most common and aggressive primary brain tumor in adults, and its poor prognosis, is a significant public health challenge. The majority of GBM’s is often difficult to operate, because of their location and infiltrative growth pattern, and nonsurgical treatments (chemo- and radiation therapy) are often ineffective. As such, relapse is almost certain and new treatment modalities are urgently needed. Brain tumor initiating cells (bTICs) are a population of neural stem cell (NSC)-like cancer cells reported in GBM. bTICs are increasingly needed. Brain tumor initiating cells reported in GBM. bTICs are increasingly needed. bTICs in human GBM through the Notch signaling pathway.

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 enriched in cells with NSC-like characteristics and the majority of cultures, more, exhibited high Notch expression and activation. Notch inhibition by the secretase inhibitor DAPT led to reduced primary neurosphere formation. Established GBM neurosphere cultures treated with DAPT, furthermore, displayed reduced expression of the NSC marker Nestin and increased expression of markers of the 3 neural lineages, suggesting increased differentiation. When neurosphere cells 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. The overall effect of DAPT treatment was more pronounced in cultures exhibiting high Notch expression and activation, compared with cultures with low Notch expression and activation. CONCLUSION: Our results suggest that Notch signaling contributes to the stem cell-like character and tumorigenic potential of bTICs, when these display dysregulated Notch pathway activation, and that it might be possible to target bTICs in human GBM through the Notch signaling pathway.

O.27. NG2 PROMOTES RESISTANCE TO IONIZING RADIATION BY ELEVATED PEROXIREDOXIN-1 AND DNA DAMAGE RESPONSE IN GliOblastoma MuLTIFORME
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Glioblastoma multiforme (GBMs) are lethal cancers that respond poorly to radiotherapy and the mechanisms may involve stem/progenitor cells. Several studies proclaimed that brain tumors enriched in CSCs were preferentially resistant to ionizing radiation and chemotherapy as a result of altered checkpoint and DNA repair pathways compared with conventional tumors. Others have claimed that these cells are associated with increased reactive oxygen species and that this is an additional mechanism for radiation resistance. Similar the glioblastoma marker NG2 has been shown to regulate tumor response to chemotherapy, we examined whether it also affected response to radiotherapy. Quantification of NG2 expression in 96 patient GBM biopsies revealed that high expressers had shorter survival outcomes than low expressers, \( P = .02 \). Two-dimensional (2D) proteomics of 11 of these biopsies showed that peroxiredoxin-1 (PRDX-1) was upregulated in the shortest surviving patients, and was associated with reduced oxidative damage. Furthermore, NG2 expressing GBMs were highly resistant to ionizing radiation (IR) in vitro and in vivo and increased PRDX-1 levels in a dose-dependent manner. shRNA mediated NG2 knockdown did not result in 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 in a hyaluronan-rich environment, overexpression of CD44 can lead to the enhancement of proliferation, migration, and survival facilitated by CD44. We have developed a murine model of gliomas that is uniquely suited for these studies. Malignant gliomas were induced in mice by transfecting plasmids encoding SV40LgT 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 immunohistoschemistry (IHC) was developed against CD44 and SV40LgT to detect CD44 expression within the bulk tumor and the infiltrative glioma cells. IHC studies have shown remarkably similar phenotypes of CD44 overexpression in both mouse and human tumor specimens. In addition, CD44-positive tumor cells can be found infiltrating into the perivascular space in the normal brain of tumor bearing mice. In contrast to CD44+ + + rapid tumor growth, CD44−−− tumors have a significant delay in progression (median survival = 50 days). Importantly, a subset of tumors in CD44−−− mice spontaneously regressed as measured by bioluminescence. CD44 loss of function was rescued by expressing murine CD44 cDNA in cis on the NrasG12V plasmid. The significant extension of survival in CD44−−− mice is abolished when CD44 expression is rescued exclusively in the tumor cells. Therefore, glioma cells require CD44, rather than the brain microenvironment, 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 for maintaining a niche supportive of tumor cell self-renewal and survival. Ongoing studies will look at CD44 modulation of multitudinous transporter activity and sensitivity to chemotherapeutic agents because of loss of function of CD44.
O.29. THERAPEUTIC TARGETING OF THE NG2 PROTEOGLYCAN WITH MAB 9.2.27 AND ADOPТИVELY TRANSFERRED NK CELLS LYES 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 mechanisms of anti-tumor the effect. The NK cells and mAb were infused intratumourally by convection-enhanced delivery (CED) in rat brains transplanted with human GBM xenografts, as well as syngeneic rat gliosarcoma. Magnetic resonance imaging was used to longitudinally monitor the tumor growth characteristics. Combined NK + mAb targeting resulted in significantly longer survival times compared with the vehicle, and monootherapy controls (U251-NG2: log-rank test, \( P = .0081 \); U87: log-rank test, \( P = .0003 \)). Histological analyses revealed strong presence of MPO, granzyme, and IFNγ-expressing granulocytic cells in focal areas of strong necrosis/apoptosis in the NK + mAb- and mAb-treated groups. Moreover, double-labeling revealed the greatest numbers of M1-type macrophages that were ED1+; CD4+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 ED1+, CD4+ positive cells that were absent and remained 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 aminable therapy for treatment-resistant GBMs.

O.30. PHASE III ANTI-EGF-RECEPTOR ANTIBODY (OSAG-101) FOR NEWLY DIAGNOSED GliOBlastoma: SAFETY AND CURRENT STATUS
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The epidermal growth factor receptor, 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 approach directed against the intercellular signaling pathway, the ligand-binding capacity of the receptor or the specific immunogenicity of the vIII

Meningioma 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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BACKGROUD: 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: We included five WHO grade I meningioma patients with a median follow-up period of 1 yr postoperatively. Furthermore, we determined the volume of cerebral edema on pre- and postoperative (3 months) MRI scans. The contribution of cerebral edema on HRQOL was investigated by correlation analysis. RESULTS: No significant differences were found in HRQOL between meningioma patients and healthy controls. However, 76% of patients reported a high level of fatigue; 32% reported to be depressed. Both pre- and postoperative tumor-related edema volume were found to be a significant predictor of the patients’ physical and social functioning, and bodily pain. CONCLUSIONS: The present study suggests an important role for cerebral edema in HRQOL in meningioma patients. Meningioma patients with a significant amount of cerebral edema seem to be at risk for developing psychological problems and should therefore be screened neuropsychologically. Further research should be focused on the effect of treatment of cerebral edema on the one hand, and the impact of neuropsychological interventions on the other hand on HRQOL in meningioma patients with edema.

O.32. HYPOFRACTIONATED STEREOTACTIC RADIOTHERAPY OF THE OPTIC NERVE SHEATH MENINGIOMA: AN EFFECTIVE OPTION
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OBJECTIVE: The management of primary Optic Nerve Sheath Meningiomas (ONSMs) is still controversial. Surgery easily leads to a complete blindness of the affected eye. On the other hand, the role of conventional radiotherapy remains uncertain and literature lacks of data to confirm its usefulness. The aim of this study was to evaluate the level of effectiveness and safety of preoperative CyberKnife (Stereotactic, Incorporated) radiosurgery as first-choice treatment for optic nerve sheath meningiomas. METHODS: In the period between May 2004 and June 2008, we treated 21 patients affected by ONSMs, with the frameless CyberKnife system. The mean age ranged from 36 to 73 WHO grade I meningioma patients. The prescribed dose was 25 Gy prescribed to the 70%–85% isodose line. All patients were treated with a Stereotactic Radiosurgery treatment; particularly, they underwent a 25-Gy treatment in 5 fractions. Before the treatment, 3 patients had a conserved visual function whereas 11 presented a deficit of the sight or of the visual field. Seven patients were blind. Patients were evaluated both for the tumor growth control and the visual function. RESULTS: The mean follow-up period was 21 months (range 7–56 months). All patients well tolerated the procedures. Only 1 patient developed a mild optic neuropathy (remitted after a systemic steroid therapy). No others’ acute or late radiation induced toxicities were observed. The median of tumor volume was 2.8 cc (range 0.3–23 cc). No patients showed a progression disease at MRI
controls. Two patients (9%) had a partial response. No patients had a worsening of the visual function. If we considered only the patients with a partial deficit of the sight or visual field, 60% showed an improvement.

CONCLUSIONS: ONSM, frameless stereotactic radiotherapy, as previously found, is safe and effective. Tumor growth control was complete and visual function was maintained or improved. If the long-term follow-up will sustain the preliminary results, stereotactic radiotherapy could become the new first-choice treatment.

O.33. SURVIVAL AND FUNCTIONAL OUTCOME OF MENINGIOMA PATIENTS: LONG-TERM DISABILITY AND POOR SURVIVAL

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

O.34. SECOND-LOOK SURGERY (SLS) FOR Ependymoma: The ITALIAN Experience

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INTRODUCTION: Complete resection of ependymoma is associated with better DFS; smaller residues are even associated with better prognosis than “bulky” residues. According to experienced neurosurgeons, a truly complete excision of an infratentorial ependymoma is not feasible without serious risks whenever tumor arises from the floor of the fourth ventricle. SLS on smaller tumors can be associated with less dangerous anesthesiologic complications; one-third of patients has stable or progressive symptoms. The role of second-look surgery (SLS) in patients with a non-total resection of an infratentorial ependymoma is still uncertain. 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 after radiotherapy; 2 children had 3 and 1 had 4 excisions. Eleven of 22 patients obtained CR: one had only a neurologic worsening. We compared the outcome of the 38 patients CR after one surgical act with those 11 obtaining CR after more acts: both groups had 3- and 5-year DFS of 66% and 3-year freedom from local relapse was 82% and 87%, respectively. Discussion: SLS demonstrated feasible without major morbidity and results improved during 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 epidemiology and the clinical, material, pathological, and management profile of all pediatric meningiomas surgically treated during the last 35 yr 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 yr, were identified in the PALGA database, the nationwide network, and registry of histology 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 neither the histological diagnosis was a revision and confirmation of the original histology, or the original histological diagnosis was changed after revision. Thus, 69 registries (37 male, 32 female) of meningiomas were included, making this the largest study of its kind. Clinical presentation: the most common symptom was raised intracranial pressure (30%), Mean age at diagnosis was 11.7 yr (0.3–18.8). Location: most frequently on the convexity (22%); Etiology: 11 patients (16%) had neurofibromatosis type 2 and 4 patients received prior radiotherapy. Histology: 42 patients (61%) had a WHO grade I, with meningothelial meningioma as most common histological subtype. Five patients (7%) had a WHO grade III tumor. Surgery: macroscopic total resection was accomplished in 31 patients (42%) and subtotal in 15 patients (30%). Simple decompression was used in 5 patients (7%). Recurrence rate was missing in 14 patients (21%). Additional treatment: 15 patients (22%) received radiotherapy postoperatively. Follow-up: mean follow-up was 4.9 yr (0–27.8). A total of 22 radiological confirmed recurrences were diagnosed in 13 patients (19%) within a mean period of 3.9 yr (0.1–26.3). Eleven tumors recurred after macroscopic total resection. Nine patients with a recurrent tumor were first diagnosed with a WHO I (69%), none with a WHO III tumor. Six patients (9%) died as a result of their meningioma. CONCLUSION: Pediatric meningiomas are extremely rare. This is the first single country study and one of the largest childhood series on this tumor. The presentation and biological behavior is different compared with meningiomas in adults. A high recurrence rate is observed and outcome tends to be worse.

O.36. DOSE CONSTRAINT MODEL TO PREDICT NEUROCOGNITIVE OUTCOMES IN YOUNG PATIENTS WITH LOW-GRADE BRAIN TUMORS TREATED WITH STEREOTACTIC CONFORMAL 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 residual/progressive brain tumors (craniopharyngioma, cerebellar astrocytoma, charismatic hypothalamic glioma, other low-grade glioma) were...
MOLECULAR MARKERS II

O.37. CI-PERINOMS: CHEMOTHERAPY-INDUCED PERIPHERAL NEUROPATHY OUTCOMES STUDIES MEASURE STUDY
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Chemotherapy-induced peripheral neuropathy (CIPN) is a major, frequent, and potentially dose-limiting adverse event of a wide variety of chemotherapeutic agents. Despite its relevance, no formally validated instruments to assess the occurrence and the severity of CIPN have been described so far. The aims of CI-PERINOMS are (i) to evaluate through a multi-center, international collaboration among experienced neurologists and oncologists the best method(s) available to assess and monitor CIPN, (ii) to determine the validity and reproducibility of the proposed outcome measures, and (iii) to produce a CIPN-specific disability sum score based on the selection of relevant questions from a large database. The study started in January 2009 and it is planned that patients’ enrollment will be completed by December 2010 or at the recruitment of 300 patients. So far 20 European/US centers (*) received EC approval and 151 patients have been enrolled at 16 centers. According the study protocol, inter and intraindividual comparison and test–retest studies are to be performed by two investigators in each participating center on patients with a stable CIPN. The scales/instruments used in the study are: TNSc (Total Neuropathy Score, clinical version); VAS = visual analogue pain scale; PI-NRS = 11-point pain intensity numerical scale; C-ODSS = calibrated-overall disability sum score; NCI-CTC = National Cancer Institute-Common Toxicity Criteria, version 3; QLO-CIPN20 EORTC = quality of life questionnaire for CIPN; QLO-C30 = EORTC 30-item questionnaire for cancer patients; QoL-FS = quality of life personal score; and mISS = modified INCAT sensory sum-score. A small battery of nerve conduction studies is proposed to each patient, in order to compare the neurophysiologic results with those obtained using clinical methods. We are convinced that the results of this study will improve the knowledge on CIPN and will be useful in designing future studies to prevent or ameliorate CIPN.


O.38. GLUT1/SLC2A1 IS CRUCIAL FOR DEVELOPMENT OF BRAIN MICROVASCULARITY WITH BLOOD–BRAIN BARRIER (BBB) PROPERTIES IN VIVO: POTENTIAL CLINICAL IMPLICATIONS
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Glucose transporter 1 (Glut1) is expressed at high levels in the capillary endothelial cells of barrier tissues such as the blood-brain barrier (BBB). In normal brain of human, rodent and zebrafish Glut1 is selectively present in the cerebral capillary endothelium. The BBB is composed of tightly linked cerebral endothelial cells sealed by tight junctions (TJ) and adherens junction (AJ). Based on recent studies and the TJ/AJ protein that are concomitantly downregulated in human high-grade gliomas and some other situations in which BBB breakdown has taken place, we hypothesized that this molecule may play a significant role in the development of cerebral capillaries with BBB properties. The homologue Glut1 amino sequence in zebrafish is highly similar to that of human but, 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 have 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 SPHEROIDS: EXPRESSION 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 and in a study, using human brain epithelial cells (MCF10A), it was demonstrated that the interaction of TIMP-1 and CD63 is necessary for the TIMP-1 anti-apoptotic pathway. The aim of the present study was to investigate the expression of TIMP-1 and CD63 in cultured organotypic multicellular spheroids (OMS) and cell line spheroids (CLS) derived from astrocytomas in order to assess spheroid models for future studies involving TIMP-1, CD63, and 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-1061 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 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 leukemia (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 serious neuromuscular toxicity led to increased recognition 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 of the US National Library of Medicine. We recorded type of alkylat-
ing and other chemotherapy agents used, dose, concomitant or sequential
irradiation, genetic predisposition, type of myogenic tumor, cytogenetic
findings, latency between completion of chemotherapy and diagnosis of
t-MDS/t-AML, treatment, and outcome. RESULTS: We identified 39 cases
fulfilling eligibility criteria. There were 17 male and 16 female patients
gender not listed in 6) with a median age of 20 years [range 0.25–69 yr].
The most common primary tumor was anaplastic astrocytoma (9) followed
by medulloblastoma, low-grade astrocytoma (6), glioblastoma (5), and
choroid plexus papilloma (3). Twenty-eight patients developed t-MDS. Of
these, 12 progressed to t-AML. In 11 patients, t-AML was the first hematolo-
gic diagnosis. Median interval between completion of chemotherapy and diag-
nosis of t-MDS/t-AML was 17 months [range 0–29 months]. Patients received
lomustine, carmustine, nimustine, procarbazine, temozolomide, or
cyclophosphamide, or nitrogen mustard as part of their brain tumor
treatment. Thirty patients in addition received partial, whole-brain, or
cranospinal irradiation. In 3 patients, a genetic tumor predisposition syndrome
might have played a role in developing t-MDS/t-AML. CONCLUSION: Albeit rare,
the occurrence of t-MDS/t-AML underlines the importance of properly
designed clinical studies as the basis for the implementation of novel treatment
strategies. Evolution of a secondary neoplasm reflects a complex pathoge-
netic process dependent upon genetic susceptibility, environmental factors,
and treatment (exposure to ionizing radiation and mutagenic chemotherapeu-
tic agents). Studies regarding the individual leukemogenic potential of these
factors are lacking and their individual contribution and possible synergisms
remain unsolved.

O.41. CHEMOTHERAPY-INDUCED POLYNEUROPAT
H SCORE (CIPS): A NEW TOOL IN THE DIAGNO
SIS OF CHEMOTHERAPY-INDUCED POLYNEUROPAT
H SYNDROME (CIPN) (CIPA)

A. Grisold1, W. Grisold1, C. Dittrich2,3, and S. Oberndorfer1; 1LBI
SCORE (CIPS): A NEW TOOL IN THE DIAGNOS
SIS OF CHEMOTHERAPY-INDUCED POLYNEUROPAT
H SYNDROME.

INTRODUCTION: Chemotherapy-induced polyneuropathies (CIPN) are representing a therapy-
limiting factor in the treatment of different oncolo-
gic disorders. Risk factors for CIPN are difficult to identify, but the diagnosis of CIPN is impor-
tant to prevent patients from neurotoxicity induced loss of neurological func-
tion. 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
direct use is difficult. The purpose the study was to design a simple, prac-
ticable questionnaire (CIPS), which can easily be used in the clinical setting.

METHODS: The CIPS was created from elements of the validated TNS and
clinically relevant symptoms, which are not included in the TNS. It consists of five
items: paresthesia, analgesia, autonomic nervous system, numbness, and hypo-
motor function. The total score ranges from 0 to 21. Patients with colorectal carcinoma and adjuvant oxaliplatin
chemotherapy were included. All patients were treated and tested at the
Oncology Department of the KFJ-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,
13 (85%) developed a CIPN and 9 (60%) study participants an acute
oxaliplatin-induced neurotoxicity. The results showed a significant corre-
lation 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

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PURPOSE: With the advance 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 immunohistochemical standpoint. Also let us advocate the strategy to
treat RN depending on the pathological findings and from literature.

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, antiangiogulants, vitamin E, and others for at least 1-month duration. For 18 patients who were refractory to these medical treatments, we per-
formed surgical excision of the necrotic mass. The surgical tissues were analyzed histopathologically with hematoxylin and eosin (H&E)
staining and anti-VEGF immunohistochemistry. RESULTS: In all surgical
specimens, irrespective of original tumor histology and radiation modal-
ities, H&E staining showed marked angiogenesis and reactive 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 prom-
inent vasculature in this area consisted of a thin endothelium, mimicking
venules, which is identified as telangiectacies. Immunohistochemistry
indicated that VEGF was produced mainly in the reactive astrocytes in
this peri-necrotic area. There was no evidence of marked immunoreactivity
of VEGF either in the center of the necrotic tissue nor in the intact brain.
Clinically, all RN cases treated by bevacizumab and removal of necrotic
tissue showed the rapid shrinkage of the pre-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.

O.43. HOT SPOTS IN 3'-FET-PET DELINEATE MALIGNANT
TUMOR PARTS WITHIN SUSPECTED WHO GRADE II GLIOMA

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OBJECTIVE: This prospective study correlates metabolic maps of intra-
tumoral [F-18]fluoroethyltyrosine (FET) uptake kinetics with detailed his-
topathology and molecular genetic profiling in untreated gliomas with
magnetic resonance imaging (MRI)-based suspicion of a WHO grade II
glioma. Special attention was set on diagnostic accuracy of FET-PET in
noninvasive delineation of an anaplastic focus. METHODS: Individual
classification of tumor parts of interest was performed. Histopathological
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O.44. 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 allow functional 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 re-construct various tracts involved in the language system (superior longitudina-lis (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 neuroanatomical 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 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 ameliorate their function. The identification was associated with a 79% chance to develop early postoperative deficits. The rate of definite deficits (at 1 mo) was <2%. The rate and speed of recovery in the postoperative period correlated with the subcortical organization of some of the tracts, such as the SLF, and could be predict preoperatively.

The combined use of DES and DTI–FT allowed to effectively and safely trace language tracts, reduced duration of surgery, patient fatigue, and kept a high rate of patient functional integrity.

O.45. USEFULNESS OF NMR-BASED METABOLICOMICS (METABOLOME) USING THE ANALYSIS OF WATER AND LIPID SOLUBLE METABOLITES AS THE PREDICTIVE FACTORS OF MALIGNANT-TYPE MENINGIOMAS

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PURPOSE: In meningiomas which are considered to be benign brain tumors, there are malignant-type tumors. Most of these malignant-type meningiomas are histologically diagnosed anaplastic or atypical ones. However, some of malignant-type meningiomas show poor clinical courses, although histological diagnoses are benign. It is difficult to distinguish this specific group from usual benign meningioma. Therefore, we tried to gain characteristic extraction by the metabolite expression profiling using nuclear magnetic resonance (NMR)-based metabolicomics (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 19 patients died during the follow-up period. The mean age was 52 years (range 35–67 years), and 20 patients were male. The mean overall survival was 411 days (min. 51 days, max. 881 days, SD 262) and kept a high rate of patient functional integrity. The combined used of DES and DTI–FT allowed to effectively and safely trace language tracts, reduced duration of surgery, patient fatigue, and kept a high rate of patient functional integrity.

O.46. INTRAOBSERVER AND INTEROBSERVER AGREEMENT IN VOLUMETRIC ASSESSMENT OF GliOBLASTOMA MULTIFORME RESECTION

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OBJECTIVE: The aim of this study was to analyze intraobserver and interobserver agreement of manual segmentation as a method for volumetric assessment of glioblastoma multiforme (GBM) resection. METHODS: Three observers performed volumetric assessment of preoperative tumor volume (PreTV) and postoperative tumor volume (PostTV) by manual segmentation on contrast-enhanced T1-weighted magnetic resonance imaging (MRI) data sets of patients. Measurements were repeated after an interval of minimum 2 weeks. Intraobserver and interobserver variability for PreTV, PostTV, and residual tumor volume percentage (RTV) were expressed in intraclass correlation coefficients (ICC). RESULTS: Intraobserver agreement is high for PreTV (ICC > 0.99), PostTV (ICC > 0.73 – 0.94) and RTV (ICC = 0.69 – 0.94). Interobserver agreement is high for PreTV (ICC > 0.97), but low for PostTV (ICC < 0.54) and RTV (ICC < 0.52). CONCLUSION: Volumetric assessment of GBM resection seems to offer high intraobserver agreement, but low interobserver agreement. The results 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.

O.47. 18F-FLUOROTHYMIDINE (FLT) – POSTION EMISIOM TOMOGRAPHY TO DETERMINE THE PROLIFERATIVE TUMOR VOLUME IN HIGH-GRADE GLIOMA AND CORRELATION WITH SURVIVAL

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INTRODUCTION: 18F-fluorothymidine (FLT) is a tracer for positron emission tomography (PET) depicting tumor cell proliferation. Quantitative analysis can be calculated by converting the maximum standardized uptake value (SUVmax) has been shown to correlate with the Ki-67 index, time to progression, and overall survival. For estimating the proliferative tumor volume (PTV), different PET segmentation methods can be used. The aim of this study was to identify the method that best predicts overall survival. MATERIALS AND METHODS: Four different segmentation methods were used to test the power of FLT–PET for predicting survival. RESULTS: Twenty-two patients had a diagnosis of glioblastoma multiforme, 2 of anaplastic oligodendro-glioma, 1 of anaplastic ependymoma, and 1 of anaplastic astrocytoma. The tumor was resected in 17 patients and 9 patients received a biopsy. The mean age was 52 years (range 35–67 years), and 20 patients were male. The mean overall survival was 411 days (min. 51 days, max. 881 days, SD 262) and 19 patients died during the follow-up period. The PTVmax was associated with a significant better survival (P = 0.03) compared with the PTV50%, PTV60%, and PTV70% and SUVmax. ROC analysis found a threshold volume for the PTVmax of 11.4 cc (sensitivity 68%, specificity 71%). Kaplan–Meier analyses showed a significant discrimination between short and long survival (P = 0.04, log rank) for this threshold. DISCUSSION AND CONCLUSION: The proliferative tumor volume as determined by FLT–PET is associated with survival in high-grade malignant gliomas. SBR is the best method to estimate the PTV.

O.48. EARLY PROGRESSION BETWEEN SURGERY AND ADJUVANT CHEMO-RADIOThERAPY IN GliOBLASTOMA

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BACKGROUND AND PURPOSE: The assessment of early progression after surgery and before adjuvant treatment in glioblastoma (GBM) may
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 the complex consequences of the brain tumors and their treatment but also 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 = 10; with head brain n = 40). The Luria’s method of complex neuropsychological diagnostics (for children), projective drawings, Children Apperceptive Test: questionnaire of Parental Attitude, Spilberger test, and questionnaire of Posttraumatic Growth (for mothers) were used as well as interview. RESULTS: The most sensitive for the brain functions disorders in children is neuropsychological testing of visual-spatial and visual-constructive functions (in 40% of children with head brain tumors). The parental attitude to the child, actual mothers’ emotional state, intention to continue education, opportunity of social contacts are the most significant prognostic factors of the mental development and compensation of the neuropsychological disorders excluding visual-spatial and some other. CONCLUSIONS: There is the need of special educational and psycho-social programs for the children with recurrent brain tumors and their families.

O.51. A HADS DEPRESSION SUBSCALE SCORE ≥ 8 CAN HELP SCREEN FOR DEPRESSION IN ADULTS WITH PRIMARY GLIOMA
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BACKGROUND: No study has validated a screening tool for the purposes of diagnosing depression in adults with glioma. We examined whether the hospital anxiety and depression scale (HADS) discriminates between depressed and non-depressed glioma patients compared with a structured psychiatric interview. METHODS: This was a prospective, two-center, longitudinal cohort study of adults with newly diagnosed primary cerebral glioma. All subjects had a structured clinical interview to diagnose or exclude MDD. Data are presented from the first two time-points: T1 (shortly after starting radiotherapy, or equivalent) and T2 (3 months later). RESULTS: We examined 135 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 = .055, McNemar test). We found univariate associations (all χ², P < .05) between MDD and functional impairment (KPS ≤ 70), current steroid use, cognitive impairment, depression, major depression, current antidepressant prescription and/or high emotional distress (NCCN distress therapist 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 affected nearly 1 in 5 individuals during the study period. MDD persisted at reassessment after 3 months, and new cases occurred over time. These findings confirm that MDD is a consistent problem 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 who are receiving antidepressants (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 may 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.52. SCREENING FOR COGNITIVE IMPAIRMENT IN PRIMARY BRAIN TUMOR: IS THE MONTREAL COGNITIVE ASSESSMENT A MORE SENSITIVE TOOL THAN THE MINI MENTAL STATE EXAMINATION?
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BACKGROUND: The cognitive sequelae of primary brain tumor (PBT) and its associated treatments are well established. Although the mini mental state examination (MMSE) is widely used as a screening measure to detect cognitive impairment, it has limitations. This study aimed to compare a newer and potentially more sensitive screening tool, the Montreal Cognitive Assessment (MoCA), to the MMSE in a neuro-oncology population.

METHODS: A series of 40 patients with histologically confirmed PBT from Liverpool Hospital, Sydney, were recruited over a 7-month period. Both the MMSE and MoCA screening tools were administered to all patients to assess the presence of cognitive impairment. Clinical and socio-demographic data were also documented. RESULTS: There were 21 males and 19 females, with mean age of 51.3 years (SD = 15.9) and median time since diagnosis 13 months (IQR 4.0–22.8). The tumor diagnoses were: high-grade n = 11 (28%), low-grade n = 11 (28%), and benign tumors, including pituitary adenoma and meningioma, n = 18 (44%). A total of 16 patients underwent resection only, 11 patients received both surgery and radiotherapy (RT), while n = 9 were treated with a combination of surgery, RT, and chemotherapy. Thirteen patients (33%) had a history of epileptic seizures and 14 (35%) were taking anti-epileptic medications at time of assessment. Only 8 (20%) patients were taking prescribed steroids. In the assessment of cognitive function, 28 patients (70%) were deemed impaired using the MoCA, compared with 18 (45%) 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 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. Since 2003, in MAASTRO clinic, all patients are screened on the level of psychological problems (SIPP). Despite the resulting advice, not all patients make use of the psychosocial support. To improve psychosocial care, two strategies are followed: all patients are selected for counseling using the SIPP. Patients with a GBM are offered a counseling session with a social worker specialized in oncology as part of the treatment plan. The purpose of a standard counseling session is to check how the patient and his family are coping with the new situation (distress), to give psycho-education, emotional support, and practical advice and explain what the social worker can mean for them during and after treatment.

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 seizure is the presenting sign of the cerebral lesion, but late seizures may also occur. More than one-third of cases with primary brain tumors present with epileptic seizures, and the incidence at diagnosis varies with histological type and location. Another 10%–30% of patients develop epilepsy in the course of their disease. Patients who present with seizures 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 52 (33.1%) patients; 33 (21%) patients presented late onset epilepsy (during the course of disease and before the last months of life); 58 patients (37.6%) presented epilepsy in the last month before death. In 9 cases, seizures occurred in the last month of life. In 101 (82%) patients the last month of life was characterized by the occurrence of seizures despite treatment. The incidence of seizures in the last month 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 for brain tumor patients presents particular concerns with respect to other stages of disease, given the frequent difficulty to swallow oral therapy in patients dying. Oral treatment needs to be changed in advance with intramuscular or subcutaneous administrations. More studies should be addressed to the issue of epilepsy at the end of life in brain tumor patients.

O.55. INF-β SENSITIZES GLOBLASTOMA CELLS TO TEMOZOLOMIDE IN AN MGMT- AND PS1-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 by INF-β. This effect of INF-β is observed in acute cytotoxic 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 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.56. RELATIONSHIP TO DIFFERENT CELLS OF ORIGIN PREDICTS THE TGF-β RESPONSIVENESS OF GlioBLASToma CANcer STEM CELLS


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

O.57. SUNTINIB MALATE AS A SINGLE AGENT OR COMBINED WITH LOMUSTINE (CCNU) IN PATIENTS WITH RECURRENT, TEMOZOLOMIDE REFRACTORY HIGH-GRaDE GLIoMA

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BACKGROUND: Receptor tyrosine kinase signaling causes profound neo-angiogenesis in high-grade gliomas (HGGs). The KIT, PDGFR-α, and VEGFR2 genes are frequently amplified and expressed in HGGs and represent a promising target for therapeutic inhibition by the small molecule kinase inhibitor sunitinib malate. PATIENTS AND METHODS: A first cohort of patients with progressive HGGs following prior RT and temozolomide received a daily dose of 37.5 mg sunitinib until progression or unacceptable toxicity (2-stage phase II design). Following the first stage, the study was amended to recruit a second cohort of patients with secondary glioblastoma (sGB), treated with a daily dose of 25 mg sunitinib (28 out of 42 days) and CCNU (80 mg/m2 on day 15). T1 + Gd and T2-weighted MRI images were obtained to evaluate tumor response in both cohorts. In the first cohort MRI-based and dynamic susceptibility contrast (DSC)-enhanced perfusion measurements were performed before and during therapy; cerebral blood volume (CBV) and cerebral blood flow (CBF) lesion-to-normal-white matter ratios were measured to evaluate the angiogenic effects of sunitinib in both datasets. RESULTS: Twenty-one patients were recruited in the first cohort. The most frequent grade ≥ 3 adverse events were skin toxicity, neutropenia, thrombocytopenia, and lymphocytopenia. None of the patients achieved an objective response, whereas a decrease in CBV and CBF within the lesion was found with the normal brain. In 4 out of 14 (29%) patients evaluable for DSC-enhanced perfusion measurements, median time-to-progression and overall survival were 1.6 (95% CI 0.8–2.5) and 3.8 (95% CI 2.2–5.3) months, respectively. No correlation could be established between VEGFR2, PDGFR-α, and KIT gene copy numbers or protein expression and the effects of sunitinib. Three patients with an sGB experienced a regression of their glioblastoma following CCNU administration at the time of progression on sunitinib (PFS > 6 months in 2 patients). Recruitment to the second cohort is ongoing (4 patients have been recruited at present). CONCLUSIONS: Single agent sunitinib at 37.5 mg/day demonstrated insufficient activity to warrant further investigation in recurrent HGG. Investigation of the activity of sunitinib in combination with CCNU is ongoing, updated results will be reported at the meeting.

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

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The objective of this retrospective study was to evaluate the impact of first-line PCV chemotherapy on low-grade glioma (LGG) growth. For this purpose, the mean tumor diameter (MTD) of 21 LGGs was evaluated on serial magnetic resonance images before (n = 13), during and after PCV onset (n = 21). During PCV, a decrease of the MTD was observed in all patients. After the end of PCV, though at a slower rate, a continuing decrease of the MTD was observed in 20 out of 21 patients. Median duration of this
persistent decrease was 2.7 years (0–7 years). According to MacDonald’s criteria, the rates of partial and minor responses were 44% at the end of PCV (6% partial and 38% minor responses), but 75% at the time of maximal tumor response, 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-methylguaninemethyltransferase (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 failure of the responsible 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 = 54) 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 2.9 years (95% CI 2.9–3.9). Fifty-three 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 90) for MGMT promoter methylation, and 81.5% (75 of 92) for IDH-1/2 mutations. TP53 mutations were uncommon in patients with 1p/19q codeletions. None of the molecular markers was prognostic for PFS, using multivariate adjustment for histology, extent of resection, age, and gender. Similarly, none of the parameters predicted survival from first progression. Solely IDH-1/2 mutations were associated with prolonged overall survival. CONCLUSIONS: None of the studied parameters is a sen-

O.61. A COMPREHENSIVE STUDY OF THE ASSOCIATION BETWEEN THE EGFR AND ERBB2 GENES AND GLIOMA RISK U. Andersson 1, J. Schwartzbaum 2, F. Wiklund 3, S. Sjöström 1, Y. Liu 4, O.61. Quality of Life in High-Grade Glioma Patients in the End-of-Life Phase E. M. Szoo 1, I. C. Reineveold 2, H. R. W. Passmo 3, J. J. Heimann 1, L. Deelen 4, and J. M. B. Thoppeh 1; 1YU University Medical Center, Amsterdam, Netherlands; 2Academic Medical Center, Amsterdam, Netherlands; 3EMGO Institute for Health and Care Research, Amsterdam, Netherlands; 4Medical Center Haaglanden, The Hague, Netherlands

INTRODUCTION: Despite intensive treatment with surgery, chemotherapy, and radiotherapy, patients with high-grade glioma (HGG) known to interact with EGFR, LRIG2 and LRIG1 with glioma and glioblas-
toma risk. METHODS: We analyzed 191 tag single nucleotide polymorphisms (SNPs) capturing all common genetic variation of EGFR, ERBB2, ERBB2, EGFR, and VEGF. Material from 4 case–control studies with 725 glioma patients (329 of whom were glioblas-
toma 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 = .009, odds ratio [OR] = 1.67 (95% confidence interval [CI]: 1.14, 2.45). The Bonferroni correction made all values nonsignifi-
cant. One SNP, rs4947986 next to the intron/exon boundary of exon 7 in EGFR, was validated in an independent data set of 713 glioblastoma and 2236 controls, OR = 1.42 (95% CI: 1.06, 1.91). INTERPRETATION: Previous studies show that regulation of the EGFR pathway plays a role in glioma progression, but the present study is the first to find certain gene-
types of the EGFR gene may be related to glioblastoma risk. Further studies are required to reinvestigate these findings and evaluate the functional significance.

O.62. COGNITIVE DEFICITS IN PATIENTS WITH GLIOMAS IN ELOQUENT AREAS BEFORE AND AFTER AWAKE SURGERY J. F. Vork, A. J. P. E. Vincent, C. M. F. Dirven, and E. G. Visch-Brink; Erasmus University Medical Center, dept. Neurosurgery, Rotterdam, Netherlands

INTRODUCTION: Cognitive performance is an important outcome measure of brain tumor treatment. Neurocognitive deficits have an impact on quality of life. Previous neuropsychological 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 pro-
cessing speed. The presence and severity of cognitive disorders is one of the main factors in the decision procedure about awake operations. However, the effect of surgery on these cognitive deficits still needs further investigation. In the present exploratory study, a comprehensive assessment of cognitive functioning was performed before and after awake craniotomy. METHODS: Cognitive func-
tioning 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 elo-
quaint areas before and after awake surgery are scarce. The results of our study indicate that the global cognitive profile of glioma patients does not consi-
ciderably 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 cog-
nitive outcome, a 1-year follow-up is performed. Furthermore, a larger group of patients will be investigated with a protocol containing more nonverbal tests, to discern the influence of language and other cognitive functions (eg, memory, executive functions) on performance of this patient group.
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 main goal 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 relatives of patient relatives in this cohort 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%) partici-
pated 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 (33%–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
end-of-life phase was also considerably 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 interven-
tions 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 multi-
plcity 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
patients—caregiver dyads participated in this study. Most patients were
diagnosed with a GBM (n = 32). The remaining 29 patients had anaplastic oligo-
dendrogliomas (n = 9), anaplastic astrocytomas (n = 3), or WHO grade III
glioblastomas (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-G). Results showed lower QOL in caregivers (FACT-G,
M = 60.2, n = 82), as compared with general population controls, matched for age, sex, and educational level,
caregiving partners reported better physical functioning (P < .001), but poorer mental functioning (P = .002). Expectantly, partners’ feelings
of caregiver mastery (P < .001) and anxiety and depression (P < .001)
were also strongly predicted by the mental functioning of the patient.
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 function-
ing 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. Glioblastoma in Elderly Patients: Health-Related Quality of Life (HRQOL) in a Randomized Trial Comparing Extended Fractionated Radiotherapy (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 50 years of age is still 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...
O.67. HAVE CLINICAL FEATURES AND TREATMENT OUTCOME OF 166 PATIENTS WITH NEUROLYMPHOMATOSIS (NL) CHANGED OVER A PERIOD OF 36 YEARS? ASSESSMENT OF A CONTEMPORARY INTERNATIONAL PRIMARY CNS LYMPHOMA COLLABORATIVE GROUP (IPCG) SERIES AND LITERATURE CONSIDERATION

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In 2010, the IPCG published a series of 61 patients with NL. We present here our updated series of 166 patients with NL to assess whether the clinical features and treatment outcomes have changed over the last 36 years. The treatment strategy included doses of trexate in the first 76 patients and these were modified to high-dose methotrexate (HDMTX) in later patients. Radiation included craniospinal and/or focal brain irradiation. The outcomes were stratified by age, performance status, number of sites involved, and the complete remission rate was 29% and overall survival (OS) was 12% at 5 years. The median overall survival was 7 months for patients aged 60 years or less and 18 months for patients aged 61 years or more. The 5-year OS rate was 27% and the 10-year OS rate was 10% for all stages of the disease. The median survival was 14 months for patients aged 60 years or less and 42 months for patients aged 61 years or more. The current series demonstrated that the clinical features, treatment outcomes, and survival of patients with NL have not changed significantly over the last 36 years. The current series also demonstrated that the treatment outcomes are better for patients aged 61 years or more compared to patients aged 60 years or less. The current series also demonstrated that the treatment outcomes are better for patients aged 61 years or more compared to patients aged 60 years or less. The current series also demonstrated that the treatment outcomes are better for patients aged 61 years or more compared to patients aged 60 years or less. The current series also demonstrated that the treatment outcomes are better for patients aged 61 years or more compared to patients aged 60 years or less.
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, or angioplastic strategy, against GBM. Recent clinical trials 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 iv. 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, diffusion-weighted imaging (MRI) to assess tumor perfusion, and vascular permeability. After sacrifice, tumors were harvested for transcriptomic, proteomic, and metabolomic studies as well as histology and immunohistochemical analysis. RESULTS: In agreement with clinical data, we found that bevacizumab reduces vessel permeability and leakage of tracer by reducing the loss of contrast enhancement and reduced Ktrans and Vp parameters. Interestingly, bevacizumab reduced blood flow and blood volumes, while spectroscopy data point at increased lactate concentration in treated tumors. A reduction in vessel number was observed while the extent of cell infiltration in the parenchyma 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. A novel model of tumor cell plasticity involving a metabolic switch will be discussed.

O.71. THE QUEST FOR HUD-SPECIFIC T CELLS: ATTEMPTS TO GENERATE A HUD-SPECIFIC T-CELL LINE

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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 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 (DC), and DCs loaded with HuD protein, HuD peptide fragments mix (protein–spanning, overlapping 15-mers), P665 protein, or P663 peptide mix were added to the subsequent cultures. Readout by intracytoplasmic IFN-γ production and addition of loaded DCs was performed at day 11, 21 and 31. In 3 of 3 subjects, a positive response to P665 peptide mix, and in 2 of 3 a positive response to P663 protein was found. However none of 3 patients showed a significant response to the HuD protein or HuD peptide mix. In the second experiment, PBMCs were drawn from 4 patients with a definitive diagnosis of Hu–PNS and loaded in 4 parallel cultures. These cells were stimulated with IL-2, and peptide-loaded autologous PBMCs were added every 2 weeks using the same peptides as in experiment 1, except P665 protein. Readout was performed every 2 weeks by flowcytometric intracellular IFN-γ and TNF-α staining. This regimen was continued 8–12 weeks. None of the 4 patients showed positive results to HuD protein or peptides. One of the patients was CMV seropositive, and indeed showed IFN-γ production upon stimulation with P665 mix. These experiments show that, although our methods were successful in the context of an experimental infection, these methods are not suitable for the induction of an HuD-specific T-cell line, nor detection of HuD-specific T cells. Either the culture strategy does not stimulate HuD-specific T cells properly, or our readout method is not sensitive enough. Therefore, we recently started using an autologous feeder system, lowered the interval of adding stimulator cells to 1 week, and additionally performed readouts using flowcytometric CD107a and CD137 staining as markers for degranulation and T-cell activation. If successful, HuD-specific T-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 vivo.
homozygous microdeletions, in PTPRD in PTPRQ, which is one of the members of the urokinase plasminogen activator receptor system. We identified that the uPARAP protein is expressed in 4 of 4 (100%) glioma samples regardless of its World Health Organization grade, but did not express in normal brain control. Introduction of 2 independent small-interfering RNAs targeting different glioma cell lines (KNS42 and KNS81), suggests that RNA interference-mediated downregulation of uPARAP into 2 different glioma cell lines (KNS42 and KNS81), resulted in downregulation of uPARAP. Boyden chamber migration and invasion assay showed that downregulation of uPARAP decreases both invasiveness and migration property in vitro. Phalloidin staining showed that in uPARAP knocked-down glioma cells, polymeric actin began to aggregate into 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 not mediated by the degradation of the aggregation of uPARAP could be a novel anti-invasion therapeutic strategy for malignant gliomas.

P.003*. METABOLIC CHARACTERIZATION OF STEM-LIKE GLIOBLASTOMA CELL LINES
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INTRODUCTION: The biology of glioblastoma multiforme (GBM) is poorly understood, but there is currently great interest in the metabolic make-up of this cancer type. METHODS: Cell lines derived from human GBM tissue were cultured under serum-free conditions following the Cambridge Protocol, which enriches the culture with tumor competent, self-renewing cells. We used 1H-NMR to analyze the concentrations of metabolites in cell extracts and cell media for 4 stem-like GBM cell lines both before and after they had been induced to differentiate by mitogen withdrawal and addition of serum. RESULTS: Using principal component analysis, it was possible to determine the differences between the metabolic profiles of the 4 cell lines tested, and to detect significant changes in their metabolic profile after cell differentiation. Most of the metabolites contributing to these changes have now been identified. Further data mining by carbon flux analysis, which quantifies the metabolites contributing to these changes, shows that they are consistent between all 4 cell lines. CONCLUSION: Our data suggest that myo-inositol, which is present in the stem-like state, is reduced to undetectable levels by differentiation. Also several amino acids show different secretion and consumption patterns in the differentiated state compared with the initial stem-like state.

P.004*. REVERSAL OF EFFECT OF U87 DERIVED MICRO-VESICLES ON BIOLOGICAL PROCESSES OF GLIOBLASTOMA MULTIFORME
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Micro-vesicles, also known as exosomes, are extracellular, membrane-bound vesicles derived from the intraluminal membranes of multivesicular bodies (MVBs) of the endocytic pathway. These MVBs fuse with the plasma membrane, which causes the release of vesicles into the extracellular environment. Various cell types, including tumor cells, have been shown to produce micro-vesicles, which are believed to play a role in signal transduction. Recently, glioblastoma-derived micro-vesicles have been shown to contain proteins and RNA. Since micro-vesicles from different tumor cells appear to be involved in several biological processes, we set out to investigate the influence of U87 micro-vesicles on multiple biological processes, including angiogenesis and proliferation. After that, we treated U87 cells with interferon-β and isolated their micro-vesicles. These micro-vesicles were used to assess effects on the above-mentioned biological processes. We found that micro-vesicles derived from untreated cells stimulate angiogenesis of glioblastoma cells. Micro-vesicles from both cells promote proliferation. Since we found that exosome production was unchanged, we studied the fusion capacity of these micro-vesicles as well as their protein and RNA content. Differences between the untreated and treated micro-vesicles were observed. In conclusion, U87 micro-vesicles influence the behavior of glioblastoma cells. This can be reversed by treating the cells with interferon-β.

P.005*. TARGETING THE RELAPSE-INDUCING CELL POPULATION OF GliOBLASTOMA
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OBJECTIVE: Residual glioblastoma (GBM) cells that persist in the surrounding parenchyma after complete macroscopic resection represent one of the major driving forces of mortality in GBM. While exposed to postsurgical therapy, little is known on their biology. It was the goal of this study to isolate and profile these potentially relapse stem-like GBM tumor cells. METHODS: Paired tissue specimens were obtained from 33 GBM patients. Residual GBM cells were derived from experimental biopsy of the resection margin after completion of standard neurosurgery. A second tissue sample, used as an internal reference, represented the resected tumor core. Tumor cells were isolated, expanded under controlled in vitro conditions, and profiled (histology, growth kinetics, invasion studies, self-renewal analysis, qPCR, combined SNP/FISH analysis, FACs, in vitro drug–response assays, and xenotransplantation) in direct comparison. RESULTS: Sample analysis revealed residual cells as distinct malignant subentities in GBM. They fulfill the functional criteria of (rapidly proliferating, highly invasive) tumor stem cells. Stem-like GBM cells were almost exclusively detected in the routinely resected tumor core (71% of the center vs 14% of the periphery samples). Expression analysis revealed in 52 of 72 comparative measurements that mRNA levels of PDGFR-A/B, TGFβ-2, TGFβ-1, VEGF-A, VEGF-D, and/or FGF4 varied at least by 50% between core and residual cells of the same GBM patient. Also, in 16 of 25 comparative measurements, different in vitro responses to radio- and/or chemotherapy (CCNU, Temozolomide) were used. In conclusion, we identified a distinguishable subpopulation of residual tumor cells of initial surgery which may open new avenues for future diagnosis and treatment of GBM. This study was supported by BONFOR® and VW Foundation Δ.
P.006*. CARBON ION RADIATION WITH OR WITHOUT THE ADDITION OF CIGLITIDE 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. Fibronectin (Fn) and vitronectin (Vn) have recently been targeted by cilengitide (CGT), a cyclic peptide known to inhibit α5β1 and αvβ5 integrins that interact with Vn (αvβ3/5β1/5) and Fn (α5β1/3). Adopted in most glioma treatment schemes, radiotherapy and chemotherapy also showed a better outcome in gliomas with high expression of Vn 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 CGT.

METHODS: Twenty-four hours before migration experiments and FACS analyses, U87 glioma cells were irradiated with single photon doses of 1 and 10 Gy using 6 MeV photons at a linear accelerater. Particle radiotherapy was applied with an extended Bragg peak (E = (128 ± 7) MeV/n). 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 treated with or without purified CGT. After 24 h, membrane filters were stained and analyzed microscopically by an investigator blinded to experimental setup. Quantitative FACS analyses of integrin expression was performed with a BeD FACScan using PE and FITC-labeled antibodies directed against α5β1 and αvβ5. Resulting expression of U87 for α5β1 on Vn 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 CGT to photon-irradiated cells decreased transmigration through Vn- but not Fn-coated membranes. FACS analyses revealed an increased expression of α5β1 and αvβ5 following low-dose photon irradiation, which was still detected after single doses of 10 Gy. On the contrary, carbon ion irradiation alone significantly inhibited both Vn- and Fn-based transmigration and fully abrogated any migration if combined with CGT. Accordingly, expression of α5β1 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 high risk of promoting glioma cell migration on Vn and Fn. CGT may additionally be administered to counteract photon-induced hypermigration toward Vn; however, Fn-based migration is not affected by CGT. Carbon ion irradiation achieves strong inhibition of migration on both Vn and Fn, which is further increased by combination with CGT. 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

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All schwannomas, 50%–60% of meningiomas, 29%–38% of ependymomas, and all tumors as part of the inherited tumors disease 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 in vitro models for human schwannoma, we showed the overexpression/activation of platelet-derived growth factor receptor β (PDGFRβ) and ErbB2/3, which is a strong activation 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 PDGFRβ and ErbB2/3, and kinase dependent 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 of ERMK/2/3. AKT/FAK basally 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 the ErbB-pathways are not the only targets of IGF-I/II, but also IGF-I/II 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 dissociation of respective pathways that seem crucial for any educated drug therapy being it mono or combinational therapy.

P.008. DOES BIPARTITE CLUSTER OF 7 + 46 MICRONAS ON CHROMOSOME 14q32.31 PLAY A ROLE IN GLOMIGENEISIS?

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BACKGROUND: We demonstrated that glomas 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 glomas and nontransformed NPCs have not been established yet. The bipartite cluster of 7 + 46 miRNAs on chromosome 14q32.31 was uniformly downregulated in all glomas tissues as well as in NPCs. This region is frequently deleted, or genetically altered, in glomas and in other haematopoetic 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 this cluster in glioma cell migration. METHODS: We recently demonstrated that photon irradiation enhances tumor cell migration. Therefore, we evaluated the role of the investigated miRNAs, we cloned the pre-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. U87 MG glioma cell line was transduced 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 2 of the tested miRNAs (14q32miR1 and 14q32miR2) induced spherical-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 glomas. Further investigation is needed to unravel the role of these miRNA on invasion, soft agar colony formation, and apoptosis and is currently tested in vitro and their effect on tumorigenicity is investigated in vivo.

P.009. BIM MEDIATES GEFITINIB-INDUCED APOPTOSIS IN GLIOBLASTOMA CELL LINES EXPERIMENTAL setting.

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BACKGROUND: Tyrosine kinase inhibitors (TKIs), as gefitinib, are currently been 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/Akt 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, SF67, and T98G) were treated for 48 hours with 10 μM of gefitinib or with solvent DMSO alone in a serum-free medium with 100 μg/mL of EGF. Apoptosis was assayed by flow cytometric analysis by Annexin V-FITC staining. Protein and expression of p-Akt, Akt, p-Erk, Erk, and tubuline were performed by Western blot (WB) using total protein lisates 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 IRDye680/800CW-conjugated secondary antibodies and quantification of proteins bands was carried out with Odyssey (Licer Bioscience) software. Bim gene copy number (BCL2L11) was analyzed by multiple Ligation-dependent Probe Amplification Sequencing analysis of exons 18–21 of EGF were done. RESULTS: None of the cell lines showed EGFR mutation in exons 18–21 and none of them showed deletion or gain of BCL2L11. Two of the 7 cell lines (SF767, U118) suffered apoptosis after treatment with gefitinib. These cell lines showed a decrease in Akt and Erk phosphorylation, increased Bim expression from cytoblot (WB) and decreased from EGF treatment after expression. Among 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.
might be crucial for glioma migration and possibly invasion. TGF-β-RNA by RNA stabilization. Together with our recent results that show bind RNA. Thus, we suppose LDH-A could influence the level of TGF-β.

We demonstrate, for the first time, that knockdown of LDH-A can decrease the RNA and protein level of TSP-1 and consecutively the processing of TGF-β. THBS-1 leads to an increased level of activated TGF-β2 that

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-β (TGF-β2) is a key regulator of invasion in high-grade gliomas, partially remodeling the extracellular matrix (ECM) and inducing proteases. Thrombospondin-1 (THBS-1), which is an extracellular matrix protein and an important angiogenesis activator 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 transfecting glioma cells with small interfering RNA directed against LDH-A (143 BIPARTITE MICRORNA CLUSTER, AND ITS RELATIONSHIP TO OTHER MOLECULAR MARKERS IN 95 GLIOMAS

BACKGROUND: We demonstrated that the large 7 + 46 bipartite Dklt-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 these microRNAs from the Dgcr3 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 microarray and qPCR analysis was performed on DNA that was extracted from paraffin-embedded samples of 95 gliomas. LOH of 14q32.31 is evaluated by using D14S65 at 14q32.32 and D14k22 at 14q32.31 markers. The analysis includes 39 oligodendrogliomas (54% WHO grade II) and 55 astrocytomas (45% 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.

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-β (TGF-β2) is a key regulator of invasion in high-grade gliomas, partially remodeling the extracellular matrix (ECM) and inducing proteases. Thrombospondin-1 (THBS-1), which is an extracellular matrix protein and an important angiogenesis activator 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, c-Jun, and THBS-1 and consecutively the processing of TGF-β2. Additionally, knockdown of LDH-A decreases the RNA level of TGF-β2. Both results may contribute to an enhanced level of TGF-β2 and increased migration, given that LDH-A is expressed. An increased expression of THBS-1 can be found in astrocytic gliomas, 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.

INTRODUCTION: 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 transfectants (U251-KIT) was evaluated using simple scratch test and matrigel invasion assays. Downstream signaling changes involving JNK, c-Jun, c-Src, and CAS were determined by Western blot. The dual 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 JNK signaling cascades and through downregulation of the c-Src- and CAS-signaling pathways.

INTRODUCTION: Lactate dehydrogenase-type A (LDH-A) is a key metabolic enzyme catalyzing pyruvate into lactate and is excessively expressed in several human tumors. Transforming growth factor-β (TGF-β2) is a key regulator of invasion in high-grade gliomas, partially remodeling the extracellular matrix (ECM) and inducing proteases. Thrombospondin-1 (THBS-1) is an extracellular matrix protein important for angiogenesis 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, c-Jun, and THBS-1 and consecutively the processing of TGF-β2. Additionally, knockdown of LDH-A decreases the RNA level of TGF-β2. Both results may contribute to an enhanced level of TGF-β2 and increased migration, given that LDH-A is expressed. An increased expression of THBS-1 can be found in astrocytic gliomas, a mechanism well known from several human cancers. Recent paper showed that LDH-A is able to bind RNA. Thus, we suppose LDH-A could influence the level of TGF-β2 RNA by RNA stabilization. Together with our recent results that show that TGF-β enhances migration in high-grade gliomas, we demonstrate a new panel of interactions between lactate metabolism and TGF-β2 that might be crucial for glioma migration and possibly invasion.
of these processes. We have demonstrated previously that the simultaneous downregulation of uPAR and UPI causes the activation of the extrinsic apoptotic pathway involving the mitochondrial Δψ collapse. From Western blot analysis of nuclear extracts from glioma cells (SNB19, U87) and xenografts (4910, 5310), we observed that uPAR is localized in the nucleus of these cells. Further analysis by immunoprecipitation, immunohistochemistry and transcription factor array revealed that uPAR was strongly associated with EGR-2 among other nuclear molecules. As determined by Western blot analysis of cytoplasmic extracts, RNAi-mediated downregulation of uPAR caused the activation of BAK expression and release of cytochrome c into the cytoplasm in SNB19, U87, and 4910 cells, and to a lesser extent, in 5310 cells. Downregulation of both uPAR and BAK retarded mitochondrial Δψ collapse from tumors derived from Mito-PT engrafted mice. With 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 187 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 were 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. Twelve percent of all referrals were received on a Friday. Up to 30% of all referrals were received from within the same hospital trust and increased significantly if the medical departments (which refer 60% of patients) were present on site (P < 0.05). Up to 27% of patients had focal neurology at the time of referral and 70% of the departments had a Glasscock score > 3. Fifteen percent of all the emergency tumor referrals were admitted to the neurosurgical unit and only 3 patients were operated upon out-of-hours. CONCLUSIONS: The majority of referrals of patients with suspected brain tumors are received during normal working hours. Most are from medical departments in the catchment area and most patients have good neurological status. Streamlining referral pathways to the neuro-oncology multidisciplinary team during working hours will improve services for patients and reduce the workload of the on-call neurosurgeons.

P.017. WHO GRADE II GLIOMA DISTRIBUTION ON THE FRENCH TERRITORY: PRELIMINARY DETAILED RESULTS CONCERNING 6 REGIONS (ALSACE, BOURGOGNE, CHAMPAGNE/ARDENNES, FRANCHE, CONTE, LANGUEDOC ROUSSILLON, AND LORRAINE)
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Diffuse infiltrating WHO grade II gliomas are relatively rare tumors. They account for 10%–15% of all gliomas with an incidence rate of 1 in 100,000 person-years, approximately. Epidemiological data are very rare, 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 neuro-oncologists, neuro-pathologists, and neuro-radiologists, after consultation with epidemiologists and biostatisticians, have established the French Brain Tumor Database (FBTDB) which is the biggest database concerning primary central nervous system tumors (PCNST) in Europe. This database continues to record all PCNST in France for which histological diagnosis is available. One of the major aims of this structure is to allow the realization of epidemiological studies. The methodology used for the geographic distribution analysis was simple: (i) identification of all the histological cases of glioma diagnosed between January 1, 2006 and December 31, 2009; (ii) for each glioma, WHO grade II glioma cases, collection of the following address (postal code) of the patient at the moment of the surgical procedure; and (iii) description of the geographic distribution of all cases in the French territory with the search of spatial clusters. RESULTS: We analyze at present inter-regional distribution of all WHO grade II gliomas from 6 regions (Alsace, Bourgogne, Champagne/Ardennes, Franche-Comté, Languedoc Roussillon, and Lorraine) corresponding to a population of 11 million of inhabitants. Preliminary results seem to show an important intraregional heterogeneity. The analysis at a national level is in progress. CONCLUSION: This original study aims to describe the geographic distribution of the WHO grade II gliomas at the level of the French territory. We will present the preliminary results concerning a population of approximately 11 millions of inhabitants.
EORTC-NCIC NCT00006353 randomized phase III trial (Snipp et al., NEJM) demonstrated significant improvements in survival yielding 16.0% long-term survivors. The present study aims to analyze to what extent these improvements within the setting of clinical trials translated to the population level. PATIENTS AND METHODS: A population-based survey on primary GBM cases, newly diagnosed in 2005, was conducted by the Austrian Brain Tumour Registry. The patient cohort was followed-up until December 12, 2018. Only GBM cases with survival time >15 years were excluded. Survival analyses were performed according to Kaplan–Meier with two-sided log-rank tests. RESULTS: A total of 375 adult primary GBM cases were identified, referring to an age-standardized incidence rate of 4.3 in 100,000 person-years (2.2–3.0) in females (WHO world standard population). Median age at diagnosis was 63.8 years, range: 18–87.0 years. Overall survival (OS) of the total cohort was 39.2% (34.3%–44.1%) at 1 year, 20.0% (16.1%–24.2%) at 2 years, and 15.5% (12.0%–19.3%) at 3 years. Significant differences in OS (P < .0001) were encountered between age groups 18–69 (n = 237, 68.5%) and 70+ (n = 118, 31.5%). Whereas in the age-group 18–69, the OS was 47.9% (41.6%–53.8%) at 1 year, 26.1% (20.9%–31.6%) at 2 years, and 19.8% (15.2%–24.9%) at 3 years, the respective rates of the age-group 70+ were 20.3% (13.6%–28.0%), 6.8% (3.2%–12.3%), and 5.9% (2.6%–11.2%). CONCLUSIONS: We show, for the first time, at the population level that GBM survival has increased when compared with historic data. The increase in survival is most prominent in the age group 18–69, whereas it is still poor in patients aged 70+. This favorable development at the population level seems to be because of innovations in diagnosis and therapy of brain tumors in the past decades, including the recent introduction of combined postoperative radiochemotherapy as new therapy standard in GBM.

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 patients had a diagnosis of glioblastoma. NOSN involvement at the time of initial consultation occurred in only 3% cases but rose to involvement in 93% cases during treatment. The NOSN had 705 contacts with patients and carers and dealt with 826 diverse issues, including clinic scheduling, symptom management, medication/steroids, psychological support, and referral to other agencies. Subsequently, the NOSN had 941 contacts with other health professionals (17 different agencies) to take forward patient care. CONCLUSION: The NOSN plays a key role in the management of patients with malignant glioma. This study indicates the high workload of the NOSN and their pivotal role in the management of this complex patient group.

P.019. NEOPLASTIC DIAGNOSIS TIMING PROFILE IN VON HIPPEL–LINDAU’S DISEASE: A PERSONAL SERIES EVALUATION
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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 intracranial tumors, 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 23 years of age. Spinal HGBs have a later diagnosis, beginning at 9 years of age, with a median at 37. PGLs diagnosis begun at age 11, with a median diagnosis age of 33. ELSTs begun 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. CONCLUSIONS: In von Hippel–Lindau’s disease, the neoplastic occurrence begins at early age. Tumors are diagnosed in 20% of affected patients before age 19. A precocious diagnosis does not predict a more aggressive clinical course in relation to other clinical signs. On the other hand, the clinical temporal profile 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 usually following patients, in order to obtain an early diagnosis and adequate management of these neoplasms.
before surgery and follow-up and a high proportion of patients had a good motor speed. Cognitive function did not differ between the evaluation periods in language competences or in memory abilities that hardly emerged months after surgery. This neuropsychological evaluation often revealed deficits in attention, language, and memory) was evaluated by means of a neuropsychological battery that allows a careful evaluation of patients and right and left hemisphere were evaluated. We have developed an extensive study how patients after surgery perceive their functional status and social and recorded in an interview setting before awake craniotomy. Three patients with preoperative language disturbances are at-risk for more persistent aphasic disturbances; therefore, more insight into this subject is warranted. Patients with preoperative language disturbances are at-risk for more persistent aphasic disturbances; therefore, more insight into this subject is warranted. 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 an objective 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.


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 ($P < 0.01$) 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 component might be involved too. Our next step is to perform a fine-grained analysis of the spontaneous speech of LGG patients on the main linguistic levels: semantics, phonology, and syntax. Our goal is to select the sensitive parameters for improvement and deterioration of linguistic behavior of brain tumor patients pre- and postoperatively. A spontaneous speech analysis might be a more sensitive tool to detect language problems than structured language tasks, such as naming, all linguistic levels are involved.

P.026. CARING FOR A PATIENT WITH A MALIGNANT GLIOMA: A STUDY OF THE CAREGIVER 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 impact of the caregiver experience. METHODS: Patients with MG within 6 months of initial diagnosis or relapse were eligible for this study if they had an involved caregiver. The Caregiver Quality of Life Index-Cancer (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 3 most strongly reported were increased levels of stress, distress over seeing their loved one deteriorate, and an increased fear of their loved one dying. The caregivers surveyed in this study scored an average of 80.6 on the 140-point scale. This is significantly lower (P = .01) than the average for caregivers across all cancers (93.3). We also found a significant difference between caregivers of patients with newly diagnosed vs recurrent MG. Caregivers of newly diagnosed patients were significantly more likely to feel sadness (P = .055) and feel that their life is imposed upon (P = .002), while caregivers of patients with recurrent MG were significantly more satisfied with their sex lives (P = .03). CONCLUSIONS: Results demonstrate the heavy burden placed on caregivers of patients with MG, particularly for those caring for newly diagnosed patients. This burden is greater than that experienced by caregivers of patients with other cancers; this may be related to the neurologic comprise of patients with MG. Caregivers play a crucial role in assisting MG patients; these find-...
RESULTS: None of the patients showed side effects during or after the strength examinations. Handgrip strength of right hand/left hand measured for Patients 1–3: 16–62/10–44 (range) lb. Handgrip strength of (dominant) right hand increased in Patients 1, 2, and 4 (+9%–+10%), and decreased in Patient 3 (−37%). Handgrip strength of left hand decreased in Patients 1–3 (−20% to −70%) (range), and increased in Patient 4 (+17%). Peak torques/weight (PT) of right knee extensors were in Patients 1–3: 91–290 (range) Nm/kg; PT of left knee extensors were 128–311 (range) Nm/kg. PT of right knee flexors were in Patients 1–5: 32–182 Nm/kg; PT of left knee flexors were 28–187 Nm/kg. At follow-up, isokinetic strength of knee extension and knee flexion decreased in 3 patients: extension of right knee increased to 9%. Extension of left knee decreased in all 4 patients (Patient 1–4: 3(−28% to −32%); Patient 4, the value increased 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 important in GMB 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 thermodestruction 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, vardenafil, oxandrolone), 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 evidences that early differentiation complex rehabilitation treatment effectively corrects neurological abnormalities and provides high quality of live of patients with LGG.

P.031. THE NEURO-ONCOLOGY SPECIALIST NURSE: COORDINATING THE CARE OF PATIENTS WITH INTRACRANIAL TUMOR
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INTRODUCTION: In 2006, the National Institute for Clinical Excellence (NICE) published guidelines in the UK for the management of adult patients who are affected by brain tumors. The guidance advises that all patients diagnosed with an intracranial tumor should be allocated a “Key Worker” to coordinate their care. In most neuro-oncology units in the UK, this role is undertaken by the neuro-oncology specialist nurse (NOSN) and the majority of nurses are single-handed practitioners. OBJECTIVE: To identify the involvement of the NOSN in the management of patients with brain tumor. METHODS: Retrospective casenote review of NOSN involvement in the management of newly diagnosed patients with high grade glial tumors (HGGT), low-grade glial tumors (LGGT), meningiomas and pituitary tumors attending to a single neurosurgeon in the period July 1, 2008–June 30, 2009. RESULTS: The records of 140 adult patients were reviewed (59 M: 81 F); The most common tumor types were HGGT (37%) and meningioma (31%). The frequency of NOSN involvement in patient management was: HGGT 87%; LGGT 69%; meningioma 51%; pituitary tumor 48%. Patient and carer contact with the NOSN was greatest in the HGGT group with an average of 13 contacts. As a consequence, these contacts the NOSN liaised with 10 other health professionals on average. Patient and carer contact was lowest in the meningioma and pituitary tumor group. CONCLUSION: NICE guidance recommends that all adult patients with brain tumors should have NOSN involvement in their care. This study suggests that we are nearing compliance in patients with compliance HGGT but there is still unmet need in patients in other tumor groups. There is a need to increase the number of NOSNs.

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.

IMMUNOLOGY AND IMMUNOTHERAPY

P.033*. INTENSE HUMAN CYTOMEGALOVIRUS (HCMV) IMMUNE RESPONSE IN GliOBlastOMA PATiENTS: A NOVEL PROGNOSTIC FACTOR FOR SURVIVAL
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BACKGROUND: Glioblastoma is a lethal malignant brain tumor with overall survival rates of < 9.8% at 5 years. HCMV is a ubiquitous human herpesvirus found in nearly all humans worldwide with a persistent infection occurring in over 70% of adults. HCMV has been implicated in the development of several human malignancies owing to oncomodulatory effects of HCMV infection. It has been recently recognized that there exists an association between HCMV and malignant gliomas. Expression of HCMV nucleic acids and proteins has been described in >90% of gliomas in vivo. To study the prognostic value of anti-HCMV immune response in glioblastoma we prospectively assessed the levels of serum HCMV IgM and IgG in newly diagnosed glioblastoma patients and correlated the results with the clinical course. MATERIALS AND METHODS: Serum from 24 glioblastoma patients treated with standard chemo-radiotherapy in our institution between November 2008 and October 2009 were analyzed. Any HCMV IgM over 0.5 U/mL was considered diagnostic for acute HCMV infection. HCMV IgG ≥ 16 U/mL was regarded as positive for latent infection. Intense HCMV IgG immune response was defined as HCMV IgG > 100 U/mL. All clinical and pathological data were recorded in a database
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 (OV) 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 and limits their therapeutic potential. It is therefore crucial to understand the mechanisms regulating anti-viral immunity to improve the OV efficacy. We have previously shown that intratumoral injection of OVs induces infiltration of phagocytes (macrophages and microglia) that inhibit viral replication and persistence. Pretreatment of animals with cyclophosphamide (CPA) depletes macrophages from the brain and microglia) that inhibit viral replication and persistence. Pretreatment of animals with cyclophosphamide (CPA) depletes macrophages from the brain and microglia) that inhibit viral replication and persistence. Pretreatment of animals with cyclophosphamide (CPA) depletes macrophages from the brain and microglia) that inhibit viral replication and persistence.

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

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There is a need for new strategies to target GBM that presents strong potential for a synergistic treatment outcome. The use of pre-existing OV-specific T cell responses in glioma patients would present a therapeutic option. We used automated two-dimensional protein fractionation (2DxSE) to identify novel tumor antigens in glioblastoma tissues.

P.036. HUMAN GLIOBLASTOMA CELLS DERIVED FROM NEUROPHIRES ARE MORE SENSITIVE TO NK, LECTIN-DEPENDENT, ANTIBODY-DEPENDENT, IL-2-ACTIVATED NK CELL LYSIS AND ANTI-TUMOR T-CELL CYTOTOXICITY COMPARED WITH CELLS FROM ADHERENT CULTURES DERIVED FROM IDENTICAL GBM PATIENTS

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Glioblastoma multiforme (GBM) is a brain tumor with a very poor prognosis as a result of inevitable recurrence. During the past few years, a contingent of cells within tumors, so-called stem-like tumor cells (STC), has been characterized in GBM. These cells have similar properties to neural stem cells and can, with a limited number of cells injected in vivo in animals, reconstitute entire tumors. STC are also resistant to current radio- and chemo-therapeutic treatments in vitro. Therefore, STC are considered to play a key role in GBM recurrence observed in patients. These cells may be appealing targets for new therapeutic approaches such as immunotherapy.

In this study, cells obtained from GBM specimen were grown in DMEM 10% FCS (adherent culture) and in serum-free medium supplemented with EGF and basic FGF (neurophores culture). Phenotypic analyses confirm expression of stem cell markers such as CD133, nestin, and A2B5 on cells from neurophores but not on cells from adherent cultures using cell lines derived from 5 different GBM patients. Expression of HLA class I molecules is observed in cells from both neurophores and adherent cultures. Regards tumor antigen expression, IL13Rα2 is expressed on cells from neurophores but not on cells from adherent cultures.

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

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BACKGROUND AND OBJECTIVE: There is increasing evidence sustained the hypothesis that human gliomas originated from glioma-initiating cells or stem cells (GIC/GSC). And usually these cells could not be eradicated by conventional surgery, chemotherapy, and radiotherapy because of their stem-like properties. The cytotoxicity of activated NK (NK) cells against GIC in vitro was investigated.

METHODS: The CD133+ glioma
cells were isolated from resected human glioblastoma specimens or glioma cell line and were used as GIC. The NK cells were separated from peripheral blood mononuclear cells of glioma patients or healthy donors by Miltenyi magnetic beads and were activated with IL2/PHA. Their in vitro cytotoxicity against GIC was assessed by lactate dehydrogenase (LDH) assay, with K562 cells as positive control target cells. RESULTS: The allogeneic NK cells could be cultured and activated with GIC-cultured medium, the increased cytolytic activity against GIC was shown with the higher E:T ratio. At the same E:T ratio, the activated NK cells showed remarkable higher cytolytic activity against GIC than that of resting (freshly isolated) NK cells (P < .01). CONCLUSIONS: The allogeneic NK cells could be activated in the GIC culture system and showed killing effect against GIC. It was suggested that activated NK cells might be used in the clinic for GIC eradication.

IN VITRO/IN VIVO MODELS

P.038*. ESTABLISHMENT OF 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, human U87, U251, U373, T98G, A172 and mouse glioma cell line (GL26) were repeatedly treated with TMZ at lower concentration (25 μM) and gradually at higher concentration (800 μM) every 4 days for about 2 months. MGMT expression of the cells was analyzed by Western blot. RESULTS: TMZ resistance developed in all the TMZ-sensitive cell lines without MGMT expression (U87, U251, U373, A172, and GL26) except in TMZ-resistant T98G cells with MGMT expression and mutant type p53. The degree of resistance to TMZ appeared about 2-3-fold higher than that of normal glioma cell lines. No difference was found in MGMT expression level between TMZ refractory cells and normal cells. The drug resistance and MGMT expression were not affected by the cell passage number. CONCLUSION: The newly established cell lines would be useful in the development of in vitro and in vivo TMZ-resistance experimental model.

P.039*. HIGH-RESOLUTION NMR SPECTROSCOPY OF BRAIN-DERIVED STEM CELLS

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NMR spectroscopy of living organisms provides a noninvasive and comprehensive insight into cellular composition and metabolism. In addition, identifying cell-specific NMR spectroscopic signals and patterns may lead to in vivo detection and tracking of different cell types including stem cells. We established high-resolution 1H-NMR spectroscopy of several cultured brain-derived stem/progenitor cell lines like Notin-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 (i.e., so-called mobile lipids and mobile proteins, regarding their stem cell specificity and their response to targeted modulation of proliferation and differentiation, for example, by means of transforming growth factor β [TGF β]). Subsequently, high-resolution NMR spectroscopy of cultured brain-derived stem cells may contribute to the key link between the fundamentals of stem cell 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.

PREDICTIVE BIOMOLECULAR MARKERS

P.040*. SCREENING CHEMOTHERAPY AGENTS USING SURGICALLY OBTAINED BRAIN TUMOR SPECIMENS

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

P.041*. STROMAL-DERIVED FACTOR 1A (SDF-1A), A HOMING FACTOR FOR MESENCHYAL PROGENITOR CELLS, IS ELEVATED IN TUMOR TISSUE AND PLASMA OF GLIOMA PATIENTS

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Malignant gliomas are a fatal disease without sufficient possibilities for early diagnosis and a lack of chemical markers to detect remission or relapse. The recruitment of progenitor cells like mesenchymal stem cells (MSC) is a main feature of gliomas. SDF-1, a chemokine produced in glioma cell lines, enhances migration in MSC and was associated with cell survival and apoptosis in gliomas. Therefore, this study was performed to evaluate (i) whether SDF-1 and its receptors are expressed in human malignant glioma in situ and (ii) if SDF-1 might potentially play a role in recruiting MSCs into human glioma. In glioblastoma tissue, immunohistochemistry revealed that SDF-1 and its receptor CXCR4 are expressed in regions of angiogenesis and necrosis, qPCR showed that SDF-1 is elevated and public expression data indicate that CXCR4 is upregulated. The latter data also illustrate that SDF-1 could be up- or downregulated in glioma compared with normal brain in a transcript-specific manner. In plasma, SDF-1 is elevated in glioma patients. The level is reduced by 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 and its receptors are expressed in human malignant glioma in situ and (ii) if SDF-1 might potentially play a role in recruiting MSCs into human glioma. In glioblastoma tissue, immunohistochemistry revealed that SDF-1 and its receptor CXCR4 are expressed in regions of angiogenesis and necrosis, qPCR showed that SDF-1 is elevated and public expression data indicate that CXCR4 is upregulated. The latter data also illustrate that SDF-1 could be up- or downregulated in glioma compared with normal brain in a transcript-specific manner. In plasma, SDF-1 is elevated in glioma patients. The level is reduced by 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 and its receptors are expressed in human malignant glioma in situ and (ii) if SDF-1 might potentially play a role in recruiting MSCs into human glioma. In glioblastoma tissue, immunohistochemistry revealed that SDF-1 and its receptor CXCR4 are expressed in regions of angiogenesis and necrosis, qPCR showed that SDF-1 is elevated and public expression data indicate that CXCR4 is upregulated. The latter data also illustrate that SDF-1 could be up- or downregulated in glioma compared with normal brain in a transcript-specific manner. In plasma, SDF-1 is elevated in glioma patients. The level is reduced by 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 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.
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 normal stem cells that control spindle orientation during cell division and therefore localizes to the cytoplasmic centromeres during interphase (cASPM) and around the nucleus during mitosis (nASPM). In this study, we correlated its expression in a tissue microarray (TMA) comprising samples of 334 gliomas to WHO grade, the proliferation marker Ki-67, and patient outcome. METHODS: Formalin-fixed, paraffin-embedded tissue samples of 283 primary astrocytic gliomas WHO II–IV and 51 recurrences were used for TMA design. Detection of primary antibodies directed against ASPM, Ki-67, and the appropriate secondary antibodies was carried out with Vectastain ELITE ABC Kit. Staining was graded semiquantitatively from 0 to 5 according to the percentage of positive cells covering the whole tissue spot. Cytoplasmic and perinuclear staining was analyzed independently. The relationship between ASPM expression, WHO grade, and Ki-67 was quantified using Spearman’s rank correlation. To examine independent prognostic confounders of survival, WHO grade, age at diagnosis, and extent of resection were included in a multivariate Cox proportional hazards regression. RESULTS: Perinuclear expression of ASPM was neither associated with WHO grade nor with patient outcome. Cytoplasmic expression of ASPM, however, resulted in a significant prolongation of overall survival (OS) both in gliomas of all WHO grades ($P = .021$) and in the subgroup of glioblastomas ($P = .026$) as well as time to malignant progression ($P = .026$) in gliomas of independent 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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INTRODUCTION: Erythropoietin (Epo) is a well-known factor of erythropoiesis and is therefore used to treat anemia in neoplastic disease. In addition, Epo exerts neuroprotective effects via Epo-receptor (EpoR) on neuronal cells. This makes a prolymphic use against neurocognitive impairment caused by radiochemotherapy probable. Epo-EpoR signaling, however, has also been recognized in various tumors such as glioblastomas. Several studies during the last years performed in vitro and in vivo reported conflicting results on the effect of Epo on malignant gliomas. We analyzed here the impact of Epo and EpoR expression on the prognosis of human glioblastomas in different treatment groups. METHODS: We established retrospectively a bank of human glioblastomas with complete documentation of clinical course and treatment. The expression of EpoR ($n = 64$) and EpoR ($n = 66$) was assessed by immunohistochemistry and analyzed with semi-quantitative scores. The results were assessed separately for short- or long-term survival in the treatment groups by univariate and multivariate analysis with respect to age, gender, chemotherapy, and extent of resection. RESULTS: High expression levels of EpoR were correlated with a median survival advantage of 8 months ($P < .01$) in patients under 60 years of age. High levels of both Epo and EpoR were associated with a significant prolongation of median survival when compared with low levels of both molecules. In patients treated with radiochemotherapy adjuvant to operation, a trend to 6-month longer median survival was observed in association with high levels of EpoR expression that just failed significance ($P = .05$). In a multivariate survival analysis, a positive correlation of EpoR expression ($P = .02$) with longer patient survival proved to be significant. DISCUSSION: In accordance with some of the previous studies, we found evidence for a longer patient survival associated with higher expression levels of EpoR in human glioblastomas. A therapeutic use of Epo for anemia in glioblastoma patients seems therefore to be safe with respect to tumor growth. A prophylactic use (i.e., for neuroprotection, however) cannot be recommended in light of the functional studies described in the literature.

P.044. METHYLATION-SENSITIVE HIGH-RESOLUTION MELTING ANALYSIS: QUANTITATIVE ASSESSMENT OF MGMT PROMOTER METHYLATION IN HIGH-GRADE GLIOMAS
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The methylation status of the MGMT (O6-methylguanine-DNA methyltransferase) gene has been shown to be a predictive marker in high-grade gliomas treated with temozolomide. 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 very sensitive technique that does not allow the quantification of MGMT DNA methylation. To evaluate the potential of high-resolution melting analysis (HRM) to detect MGMT methylation with high sensitivity and estimate quantitatively the extent of methylation in tumors, we used genomic DNA derived from 72 high-grade glioma samples and unvernal methylated/unvernalized DNA standards. After bisulfitite 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%. Methylated 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.045. THE PROGNOSTIC/PREDICTIVE ROLE OF IDH1 GENE MUTATIONS IN PATIENTS TREATED FOR RECURRENT GLIOMA
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BACKGROUND: Somatic mutations in the isocitrate dehydrogenase 1 (IDH1) gene have been frequently found in low-grade glioma (WHO grade II–III), less frequently in secondary glioblastoma (sGB), and associated with a significantly younger age and a better survival from primary diagnosis. The aim of this study was to investigate the correlation between IDH1 gene mutation status and clinical outcome in patients with recurrent glioma enrolled in phase II trials with the EGFR-targeted monoclonal antibody cetuximab and the VEGFR inhibiting small molecule sorafenib. METHODS: Somatic DNA was extracted from formalin-fixed and paraffin-embedded tumor tissues of 52 patients with recurrent glioma, 36 of which were treated with cetuximab, and 16 who were treated with sorafenib in the context of two prospective phase II clinical trials. Nested PCR and denaturing gradient gel electrophoresis (DGGE) were performed to detect IDH1 mutations; codon 132 of IDH1 was sequenced in case of an abnormal DGGE pattern. RESULTS: IDH1 mutations (G395A in 15 cases and C394T in 1 case) were found in 8 of 14 (57%) WHO grade II–III glioma, 4 of 7 (57%) sGB, and 4 of 40 (10%) dGB ($P < .05$), and were associated with a younger age ($P < .05$). Patients with IDH1 mutations had a longer progression-free survival (PFS) and overall survival (OS) from initial diagnosis ($P < .05$ for both). The IDH1 mutation status was not significant correlated with TTP or OS from the time of recurrence in the sunitinib and cetuximab studies. A trend ($P = .07$) was observed for IDH1
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 astrocytomas and oligodendrogliomas. The two isoforms catalyze the conversion of isocitrate to a-ketoglutarate with reduction of NADP+.

Mutations are preferentially located in exon 4 of both IDH1 and IDH2 genes, affecting arginine at codon 132 (R132) of IDH1 gene and the codon 172 (R172) of IDH2 gene. MATERIALS AND METHODS: Search for mutations in IDH1 and IDH2 genes was investigated in a series of 120 grade IV (glioblastomas), 32 grade III (10 astrocytomas and 22 oligodendroglias), and 44 grade I–II gliomas (10 pilocytic astrocytomas, 10 diffuse astrocytomas, 24 oligodendroglias). Analysis was performed on formalin-fixed and paraffin-embedded surgical samples by direct sequencing.

RESULTS: Distribution of IDH1 mutations was inversely correlated with histological grade, occurring in 50% of diffuse astrocytomas grade II, 10% of pilocytic astrocytomas, 75% of oligodendroglias grade II, 36% of oligodendroglias grade III, and 2% of tumors grade IV. The majority of mutations were in IDH1 gene: R132H accounting for 91% of cases, R132Q for 6% and R132C for 3%. Those of IDH2 gene (R172K) were limited to 1 glioblastoma and to 1 oligodendroglia. Associations of IDH1 mutations were tested for the following molecular markers: MGMT hypermethylation, LOH of 1p/19q, EGFR amplification, and TP53 mutations. IDH1 mutations showed a trend towards a positive association with MGMT hypermethylation and LOH of 1p/19q, whereas they were mutually exclusive with EGFR amplification (P = 0.0346). CONCLUSIONS: IDH1 and IDH2 mutations may represent an early genetic event in gliomagenesis, preceding the differentiation of precursors, and may be considered prognostic. It is conceivable that they are preserved in secondary glioblastomas. The latter must be rather rare in our collection where none of the glioblastomas was diagnosed at a second surgery after a previous astrocytoma.

P.047. SERUM S-100B PROTEIN IS A PREDICTOR OF SURVIVAL IN RECURRENT GLIOMA
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BACKGROUND: S-100B protein is raised in serum after cerebral damage and disruption of the blood–brain barrier. In a pilot study, high serum levels S-100B in glioma patients were associated with shorter survival. Our aim was to evaluate the value of S-100B in serum as a prognostic marker in tumors of astrocytic type and the response to chemotherapy.

MATERIALS AND METHODS: Serial samples of 22 patients with recurrent glioma were obtained before, during, and after chemotherapy. Serum S-100B was measured and a Kaplan–Meier curve was drawn for high and low serum concentrations (cut off value of 0.1 μg/l). RESULTS: Recurrent glioma patients with a high serum concentration S-100B at baseline had a significantly shorter survival compared with patients with a low concentration (P = 0.000). No trends were detectable in serial measurements. No correlation was found between S-100B concentration and age, gender, tumor pathology, or response to chemotherapy. CONCLUSION: In patients with recurrent glioma, serum concentration S-100B is a strong predictor for survival.

P.048. TEMOZOLOMIDE AND RADIOTHERAPY IN NEWLY DIAGNOSED GLOBLASTOMA PATIENTS: MGMT PROMOTOR 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 methyl transferase (MGMT) promoter methylation status and Ki-67 labeling index, and response to temozolomide (TMZ) treatment, with KI-67-label index, and response to temozolomide (TMZ) treatment, and survival in newly diagnosed glioblastoma (GBM) who are treated with temozolomide (TMZ) concomitant with and adjuvant to radiotherapy (RT).

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. Methyltransfer-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 seven patients till further progression was proved. RESULTS: Three patients were excluded because of a tissue sample of less than 100 mg. 21 patients (61.7%) had methylated MGMT, whereas 13 (38.7%) had unmethylated MGMT. The cut off value of Ki-67 in relation to survival was 17%, where 15 specimens were <17% (48.4%), and 16 were ≥17% (51.6%). The overall disease control rate was 74.2%, while the median overall TTP was 12 months and the median OS was 20 months, the methylated patients had a higher median TTP of 13 months (range 8–18 months, CI 95% of 9.36–12.9), and OS of 24 months (range 12–31 months, CI 95% of 16.1–21.3). In the median overall TTP of 6.5 months and a median OS of 12 months which was highly significant (P = .0001).

Patients with Ki-67 >17% had a median TTP of 16 months and median OS of 24 months compared with 7 and 12.5 months, respectively, for the patients with Ki-67 ≤17%. The multivariate analysis of both methylthion status and Ki-67 showed a nonsignificant correlation to ODC, TTP, and OS. Significant correlation was found between the ODC, TTP, and OS with age <52 years (P = .001), tumor excision vs biopsy (P = .0001), and the number of TMZ doses received ≥10 doses (P = .002). The commonest G3 and G4 toxicities were lymphopenia and neutropenia in 3 patients (9.67%), thrombocytopenia in 4 patients (12.9%), and 1 patient with G3 constipations (3%), all were medically manageable. CONCLUSION: This study showed that MGMT promoter methylation status and the Ki-67 status could serve as independent predictive and prognostic markers of response and survival, they also might identify a group of patients who could benefit from combining further therapeutic agents to the TMZ.
highest combination of sensitivity and specificity was observed for an IFP change of 0.014 percentage-points per day. At this cutpoint, the sensitivity, specificity, PPV, and NPV for prediction of significant thrombocytopenia were 60%, 67%, 76%, and 97%, respectively. CONCLUSIONS: Low sensitivit,y specificity, and PPV indicate that the time course of PLT counts and IFP measured at routine clinical follow-up are not useful for prediction of 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 major source for cytosolic NADPH production necessary for the regeneration of reduced glutathione, which functions as the main antioxidant in mammalian cells. To determine the prevalence and the prognostic impact of IDH1 mutation in gliomas, we investigated a series of 83 different tumors of different WHO grades. In addition, we examined the correlation of IDH1 mutations with MGMT promoter methylation status and overall survival. METHODS: We screened a total of 83 gliomas, including 34 glioblastomas (G3), 53 anaplastic astrocytomas (AA3), 3 diffuse astrocytomas (DA), 1 pilocytic astrocytoma (PA), 7 anaplastic oligoastrocytoma (AOA), 3 oligoastrocytoma WHO grade II (OA), 13 anaplastic oligoastrocytoma (AOG), 12 oligodendroglioma WHO grade II (OG), 3 ependymomas (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) GBs; 60% (3/5) AA; 67% (2/3) DA; 71% (5/7) AOA; 100% (3/3) OA; 61% (8/13) AOG; and 67% (8/12) OG. No mutation was present in any of PA, EP or AEP cases. Sequencing confirmed the results obtained by HRM in all 31 sequenced tumors. Two different mutations were found in codon 132: Arg132His in 19 cases and Arg132Gly in two other cases. Almost all IDH1 mutated gliomas presented MGMT promoter methylation (92%). The presence of IDH1 mutation was associated with better outcome in high grade gliomas (P < 0.01). CONCLUSION: We confirm the very high frequency of IDH1 mutations in WHO grade II and III astrocytic and oligodendroglial gliomas while the low or absent frequency of mutation in primary GBs and ependymal tumors. In addition, in this study, IDH1 mutation is an important factor associated with favorable prognosis.

P.051. MUTATIONS IN IDH1 AND TP53 AS PROGNOSTIC BIOMARKERS IN BULGARIAN PATIENTS WITH GLIOMAS

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Brain tumors, in particular gliomas, are characterized by high mortality rate. However, gliomas with similar features often show different behavior. This raises the issue about molecular markers for prognosis prediction. Recently, somatic mutations in IDH1, which encodes cytosolic isocitrate dehydrogenase 1, were reported to occur at high frequency in glioma tumors and association with overall survival was found. Genetic aberrations in IDH1 were predominantly detected in tumors that harbor TP53 mutations and mutations at codon 248 and 273 were associated with good prognosis. To determine prognostic value of IDH1 and TP53 mutations in Bulgarian patients, 30 glial tumors of various grades were selected and DNA was extracted from them. All samples were examined by direct sequencing for mutations in exon 4 of IDH1 and exon 5–8 of TP53 gene. Mutations in IDH1 were found in 8 (27%) glial tumor. All genetic aberrations were located at position 395 and caused amino acid substitution R132H. Patients with IDH1 mutations were younger (median age 35.5 vs 54 in non-mutated cases; P = 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 43.8 months, while median survival of those with mutation in one of the genes and nonmutated cases was 31.6 and 6 months, respectively. Our results indicate that together IDH1 and TP53 mutations identify gliomas with better survival and may be applied as 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 recognized as an effective mechanism for tumor suppressor gene inactivation. Runt-related (Runx) proteins are tissue-restricted and cancer-related transcription factors that regulate cell proliferation and differentiation. RUNX3, the smallest protein of the Runx family, has been shown to play an important role in neuronal development, localized at 1p36 and its loss leads to tumorigenesis. We aimed to evaluate the methylation-mediated expression regulation of RUNX3 gene in brain tumors.

Cases (10 females, 11 males) were recruited into the study that have been diagnosed as brain tumors (3 meningiomas, 3 anaplastic astrocytomas, 3 anaplastic oligoastrocytomas, 12 GBM) and taken the decision of surgical operation. The mean age was 52.43 ± 15.33. Explant cell cultures were performed. Total RNA was isolated. Real-time quantitative RT-PCR analyses of RUNX3 gene were actualized. Genomic DNA and the bisulphite modification were performed for DNA methylation analysis. Quantitative methylation-specific PCR was used and primer pairs were designed. There was no significant difference between methylated and unmethylated quantitative ratio of RUNX3 gene promoter region and gene expression relative ratio. Methylation and unmethylated ratio in anaplastic astrocytoma, diffuse astrocytoma, GBM, meningioma, and in all groups were: 1.44, 1.09, 1.51, 1.52 vs 1.43, respectively. One allele was found methylated necessarily. No methylation was detected in GBM and anaplastic astrocytoma groups of one each case. IDH1 was normal and unmethylated promoter in one of the GBM cases. There were significant differences between relative ratio of RUNX3 gene expression and methylated/unmethylated ratio rate, compared with all groups (P = 0.001) and compared with GBM groups (P = 0.041). This study overemphasized the RUNX3 gene importance in brain tumors, as a result of the existence at least one methylated allele.

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 in order to better understand which factors can predict BV efficiency. RESULTS: Eighteen recurrent MGs (glioblastoma = 7, anaplastic astrocytoma = 3, 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. Rasal sVEGF and sVEGFR levels 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 sVEGFR 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

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Malignant gliomas are the most common type of primary brain tumors affecting 16,000 new patients every year in the United States. In this study, we undertook a systematic large-scale transcriptomic data mining study of 9,783 Affymetrix samples from the Genesapens database (www.genesapen s.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 423 samples of the normal cerebral cortex system as well as all three 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 chose to validate its expression by immunostaining and functional role by 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 FML bodies by immunostaining and co-localized with the ceh-binding protein (CBP). In conclusion, these results pinpointed HES6 as a potential therapeutic target playing a critical role in sustaining glioma cell growth, survival and possibly invasion. HES6 may also be a useful biomarker for gliomas.

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NEW DRUG DELIVERY METHODS

P.054. GS-H-JCONJUGATION 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. Gluthathione (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 microanalysis 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 5-fold higher), and GSH-liposomes carrying endomorpin-1 were more effective in hot-plate tests when compared with unconjugated liposomes. We have now tested GSH-conjugated PEGylated liposomes containing doxorubicin (GS-H-Doxil) for treatment of mice carrying intracranial U87 xenografts. In a first series, we compared 5% GSH-Doxil to conventional Doxil, free doxorubicin (Ds), 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 Ds-equivalents. The cohorts receiving Doxil and Ds 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 Ds-equivalents. Moreover, 5% GSH-Doxil and 5% GSH-Doxil were tested relative to Doxil and untreated controls. Treatment started at Day 14 after tumor cell injection, stratifying only animals whose tumor BL signals increased relative to Day 11. After Day 25, the animals experienced weight loss and a precluded further treatment. In this series, the variation in 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 5% GSH and Doxil cohorts was marginally better relative to controls Overall, these results warrant further preclinical and clinical investigation using 5% GSH-Doxil liposomes.

NEUROIMAGING OF BRAIN TUMORS

P.054. ROUTINE FOLLOW-UP IMAGING AFTER TREATMENT FOR GLOBLASTOMA: HOW USEFUL IS IT?

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INTRODUCTION: Glioblastoma multiforme (GBM) is the most common and aggressive malignant primary brain tumor (MPBT). It is a 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, or 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 asymptomatic tumor recurrence. RESULTS: Of 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 between 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 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 a 4–6 monthly scans is common practice. Neither specifies the optimal timing or frequency of post treatment scans. The National Comprehensive Cancer Network (USA) recommends post treatment scans every 2–3 months post MPBT treatment, as does the Cancer Council Australia. There is lack of consensus and evidence regarding the ideal post treatment imaging in patients with MPBT. Further studies are required to evaluate clinical and cost effectiveness.
P.057* PERI-ICAL 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 occurs. The incidence and clinical impact of these pseudo-progression lesions has not been systematically assessed.

RESULTS: Growth occurred irrespective of hearing status checking the presence of central nonenhancement, VS stage and side and enhanced T1-weighted images (CE T1-WI). Morphology was evaluated by more profound, and hearing will detorriate faster in patients presenting audiological function and detoriation. CONCLUSION: Hearing loss was significant growth in the first year was predicting 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.058* CORRELATION OF VESTIBULAR SCHWANNOMA VOLUME WITH GROWTH AND AUDITORY FUNCTION IN A WAIT AND SCAN POLICY
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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 201T1 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 201T1 SPECT in the prediction of outcome in glioma patients treated with temozolomide and/or radiotherapy for newly diagnosed glioblastoma multiforme (GBM) (study A), and with temozolomide for recurrent glioma (study B). MRI and 201T1 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 201T1 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 201T1 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 201T1 SPECT are valuable in the prediction of outcome. It is adequate to restrict to one of both modalities in the radiological follow-up during treatment. Without clinical progression, we suggest to perform MRI only at the end of the standard treatment protocol in newly diagnosed GBM, and only at baseline in recurrent glioma.

P.059* MRI AND THALLIUM-201 SPECT IN THE PREDICTION OF OUTCOME IN GLIOMA THERAPY
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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 0.75 x 0.7 mm; slices = 208; parallel imaging factor = 2, TR/TE/TI = 3800/1700/3.55 ms, acquisition time = 10:29 minutes. Contrast agent was injected in the first follow-up MR investigation 2 weeks after initiation of bevacizumab therapy. In 2 patients we observed an increase of SWI signals already at the first follow-up MR investigation 2 weeks after initiation of bevacizumab therapy. Both patients developed progressive neurological worsening and bevacizumab therapy had to be suspended because of tumor progression after 6 and 8 weeks, respectively. In 1 patient showing rapid decrease of contrast enhancement and sustained clinical improvement under bevacizumab therapy.
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 BEVAZUMAB TREATMENT IN HIGH-GRADE GLEOBLASTOMA PATIENTS C. Baláša 1, V. Vallejos 1, S. Villa 1, S. Domenech 1, O. Etxaniz 1, L. Cardeal 1, and C. Hostalot 2; 1Institut Català d’Oncologia, Badalona/Barcelona, Spain; 2Hospital Universitari Germans Trias i Pujol, Badalona/Barcelona, Spain; 3Institut de Diagnostic per la Imatge, Badalona, Barcelona, Spain

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 of 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. 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 41.7%, and 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: 25%, CR: 8.3%. Coincidence between SPECT and MRI was 24.9% and SPECT with MacDonald’s criteria was 16.6%. The solitary patient with a CR by MRI and MacDonald’s modified criteria had an abnormalization of a previous positive SPECT lasting for 103+ weeks while continuous maintenance Bev. CONCLUSIONS: In spite of reduced number of patients, it seems that Thallium SPECT is not a good imaging method to evaluate response of bevacizumab treatment.

P.062*, PRESERVATION OF PYRAMIDAL TRACT BY NAVIGATION-ASSISTED INTRAOPERATIVE MAPPING IN GLIOMA SURGERY F. Yamaguchi 1, T. Kojima 2, H. Takahashi 1, and A. Teramoto 1; 1Nippon Medical School, Neurosurgery, Tokyo, Japan; 2Yotsuya Medical Cube, Neurosurgery, Tokyo, Japan; 3Nippon Medical School Musashikosugi Hospital, Neurosurgery, Kawasaki, Kanagawa, Japan

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 neuroradiologist 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 neuroradiologist 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 neuroradiologist 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 INFLAMMATION DURING ONCOLYTIC VIROThERAPY A. Klejin 1, J. W. Chen 1, P. Z. Sun 2, J. Buhrman 1, S. D. Rabin 3, R. Weisleder 1, R. L. Marza 2, and G. Fulci 1; 1Massachusetts General Hospital, Harvard Medical School, Boston, MA; 2Erasmus Medical Center, Rotterdam, Netherlands

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 efficacy of OVs is limited because of host factors. We have recently demonstrated that the capacity of OVs to spread in vivo through the tumor is inhibited by intratumoral infiltration of phagocytic microglia and peripheral macrophages. Combining OVs with immune suppressive drugs can therefore increase their spread and therapeutic efficiency. However, the lack of a noninvasive imaging technique to detect intratumoral OV spread and phagocytic infiltration constitutes an important limitation in evaluating the results of new therapeutic strategies. We have tested 2 noninvasive magnetic resonance imaging techniques. The first one uses a gadolinium-based contrast agent to detect myeloperoxidase (MPO) activity, an enzyme present in phagocytic cells. MRI images show increased MPO activity after OV delivery. This enzymatic activity is reduced when animals are pretreated with cyclophosphamide. The MRI data correlate with immunohistological staining of phagocytic cells. 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.
nerve involvement has not been described before. The majority presenting as cerebellopontine angle masses. Leptomeningeal spread occurs in 33% of cases. Extra-axial presentation in adult cases is extremely rare (annual incidence 1 per 2–20 million. Medulloblastoma is the most common pediatric central nervous system tumor, with a confirmed neurogenic origin. Final diagnosis was desmoplastic neuro-ependymoma. DISCUSSION: Within the next week, the patient developed progressive cranial nerve deficit and enhanced partially, namely in the right-sided brainstem. Repeated MRI scan 2 weeks later showed progression of the hyperintens tracts, now extending into the left pons and cerebellar peduncle. The patient underwent a navigation-guided biopsy of the right temporal lobe. 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 present. Patient deteriorated further and palliative treatment was offered. CONCLUSION: The presented case exemplifies the radiological and pathological characteristics of a high-grade glioma with involvement of brainstem, pons and thalamus. 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 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 finding 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. We describe a case of a patient with a right frontal glioblastoma. The tumor consists 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.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 multimodal brainstem lesion, in conjunction with a right temporal mass, which turned out to be an astrocytoma. To our knowledge, this kind of presentation has not been described so far. CASE DESCRIPTION: A 51-year-old male patient presented at the neurology department with dizziness, speech disturbances and a strange feeling at the left side of his face. Initial neurological examination was unremarkable, except for a dysarthria. One day after the MRI scan was performed, the patient was admitted to the emergency department because of a secondary generalized seizure. Neurological examination revealed a (post ictal) left sided paralysis and a Babsinski-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 pleocytosis or signs of malignancy. MRI showed a T2 hyperintense mass in the right temporal lobe, without enhancement after administration of gadolinium; radiologically suggestive of a low-grade glioma. Furthermore, hyperintensity along the white matter tracts in brainstem, pons, cerebellar peduncule, and thalamus was present. This white matter hyperintensity exerted some mass effect and enhanced partially, namely in the right-sided brainstem. Repeated MRI scans 2 weeks later showed progression of the hyperintens tracts, now extending into the left pons and 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 exemplifies the radiological and pathological characteristics 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.

### 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), suggested schwannoma. Steroid therapy was started, and the patient was referred and scheduled for surgery in our center. 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 subtle, 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 left-sided cranial nerve involvement. 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 axial hyperintenses. The right frontal leptomenigeal 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. 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.
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 CD133 and MGMT status, the patients were categorized into three groups. Among these three groups, patients with methylated tumors and low expression level of CD133 (group I) had the best prognosis. No benefit from chemotherapy was observed in patients with high expression level of CD133 (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) and radiation has become a standard of care in treating 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 among patients with a diagnosis of glioblastoma and treated with the addition of concurrent and adjuvant temozolomide (TMZ) and radiation. A total of 150 patients (median age: 52 years, [24–76 years]) were enrolled. MGMT methylation status, evaluable in 110 patients, was present in 38% of cases. Median OS was 18.5 months. At disease progression, 40 patients (27%) received temozolomide, 92 patients (61%) received nitrosourea-based chemotherapy, and 18 patients (12%) received other treatments. At the time of recurrence, mPFS was 2.5 months (95% CI: 2.0–3.1), mPFS 6% 15% (95% CI: 9.5%–21.3%), mOS 7.6 months (95% CI: 6.9–8.3) and OS 6% 64% (95% CI: 56.6%–72.2%). 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 that a PFS-6 of 15% should be considered 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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**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, females, median age 62 years (17–81), median Karnofsky performance index at diagnosis 70 (20–90). The log-rank test was used to evaluate the significance of the prognostic variables, and the Cox model to ascertain any association between PFS and OS. A total of 150 patients (median age: 52 years, [24–76 years]) were enrolled. MGMT methylation status, evaluable in 110 patients, was present in 38% of cases. Median OS was 18.5 months. At disease progression, 40 patients (27%) received temozolomide, 92 patients (61%) received nitrosourea-based chemotherapy, and 18 patients (12%) received other treatments. At the time of recurrence, mPFS was 2.5 months (95% CI: 2.0–3.1), mPFS-6 15% (95% CI: 9.5%–21.3%), mOS 7.6 months (95% CI: 6.9–8.3) and OS 6% 64% (95% CI: 56.6%–72.2%). 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 that a PFS-6 of 15% should be considered 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.

**INTRODUCTION:** The EORTC (26981-22981)/NCIC CTG (CE.3) RCT in newly diagnosed GBM found sustained improvement in survival with the addition of concomitant and adjuvant temozolomide (TMZ) to radiotherapy (RT). Study patients were aged 19–71 (median 56) years, and 58% had primary untreated tumors, 42% had tumors that were recurrent, or progression after TMZ failure. Median PFS was 4 months and median OS 13 months. Therefore, RT alone is considered the 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, 560 patients will be accrued in 3.7 years with final analysis after 5 years. Patients are randomized, yielding a study duration of 5 years. Study Progress: The trial is open in Canada (NCIC CTG), Europe (EORTC), Australia and New Zealand (TROG), and Japan. As of March 1 2010, 123 patients were randomized. Median
Glioblastoma multiforme (GBM) is the most common brain tumor but also the most aggressive one. Despite heavy treatment, life expectancy usually does not exceed 15 months. Therapy failure may be explained by GBM features such as high proliferation rate, invasiveness, and cellular heterogeneity. Similar to other malignant tumors, GBM appear to contain a subpopulation of cells that display stem cell properties and are able to survive in a hypoxic microenvironment. However, the mechanisms permitting stem-like cell survival under low oxygen conditions are not yet understood. Here we provide a detailed functional and molecular analysis of glioma stem-like cells grown under hypoxic conditions. Two stem cell-like cell lines NCH644 and NCH421k were compared with classical serum-dependent glioma cells (U87, U251, and U373) with regard to their behavior less than 1% and 0.1% O2 culture conditions: proliferative potential, invasiveness, and clonogenicity were investigated. Stem cell-like cells showed marked differences in their response to hypoxic conditions as compared with non-stem-like glioma cells. Low oxygen levels dramatically inhibited glioma cell division whereas stem cell-like cell proliferation was only marginally affected by hypoxia. These cells appeared to survive even when oxygen level was as low as 0.1%. The optimal hypoxia conditions were chosen for further transcriptomic analysis based on cell survival data and protein expression profile of hypoxia inducible factor (HIF-1a). The cellular response to hypoxia was studied at the transcriptomic level using whole-transcript expression analysis (GeneChip® Human Gene 1.0 ST, Affymetrix). Candidate genes for cell survival response to hypoxia were validated using quantitative PCR, protein-based approaches, and functional bioassays. Such genes may provide new molecular targets for GBM treatment by specifically targeting the glioma stem-like cell population.

INTRODUCTION: We previously demonstrated that NG2-expressing (NG2+) glioma stem-like cells (GLS) 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 functional relevance of the molecular signature of GBM-NG2+ and GBM-NG2 cells. METHODS: 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 (MCM). 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 tumorgenicity 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 MCM genes, and over activation of MAPK and Akt pathways.

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 radiochemotherapy 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 showed progressive disease in 6 subjects, partial response in 16, and stable disease in 4; 1 patient was lost to follow-up. Overall, 6/47 was 50% and 6/47 was 64%. Median PFS and median OS were 6 and 10 months respectively. For Grade III patients, median PFS was 37% and 6/47 was 65%. At baseline the number of CEGs was significantly higher in GBM patients than in AA (113.1 ± 5.7 vs 61 ± 31, P = 0.04). A significant reduction of CEGs and viable CECs was observed only in GBM patients with a clinical response and radiological response after 2 months of therapy (11.6 ± 52 vs 70.9 ± 55.3, P = 0.05 for CECs and 33.4 ± 18.3 vs 16.2 ± 16.4, P = 0.03 for CECs viable). No significant difference in CEPs number and viability among patients and during treatment was detected. The data suggest that investigations of CEC study levels could make a contribution to a better understanding of clinical responses to bevacizumab action in HGG patients.

The influence of hypoxia on glioma and glioma stem-like cells

P.075*. THE EFFECT OF HYPOXIA ON GLIOMA STEM-LIKE CELLS
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P.074*. CIRCULATING ENDOTHELIAL CELLS DECREASE BY SPECIFICALLY TARGETING THE GLIOMA STEM-LIKE CELL POPULATION
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P.073*. INFLUENCE OF HYPOXIA ON GLIOMA STEM-LIKE CELLS
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P.072*. NEOADJUVANT TEMOZOLOMIDE FOR GRADE III AND IV ATYCROTOMA: A RANDOMIZED PHASE II STUDY
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P.071*. RELAPSING HIGH-GRADE GLIOMA PATIENTS RESPONDING TO BEvacizUMAB
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Angiogenesis, the recruitment of new blood vessels, is an essential component of tumor progression. High-grade gliomas (HGGs) are highly vascularized tumors and bevacizumab, a humanized monoclonal antibody targeting the vascular endothelial growth factor (VEGF), is active in preclinical testing in vitro and in vivo. In the clinical setting, in combination with irinotecan, other chemotherapy agents or alone, it has shown significant activity in HGG patients. Therefore, the identification of patients who might benefit from antiangiogenic therapies is crucial for the optimization of treatment strategies. In other solid tumors, levels of circulating endothelial cells (CECs) and levels of circulating progenitors (CEPs), contributing to the formation of tumor vessels, correlate with the degree of tumor angiogenesis and the response to angiostatic therapy. Twenty-seven patients with recurrent HGG (22 glioblastomas (GBM) and 5 anaplastic astrocytomas (AA)) were treated at the Neurological Institute C. Besta, Milano, with irinotecan (340 or 125 mg/m2 for patients on EIAEDs or not, respectively) and bevacizumab 10 mg/kg every 2 weeks. Median age was 53 years (range 15–66) and mean Karnofsky Performance Status (KPS) was 70 (range 50–100). The median number of prior chemotherapy treatments was 2 (range 1–4). Median follow-up was 6 months. Number and viability of CECs and CEPs were measured on Day 0 and every 2 months by 6-color flow cytometry. CECs were enumerated as Syto 11+/CD 45−/CD 31+/PhlH12+ cells, whereas CEPs as Sca 1+/CD 133+/CD 45−/CD 31−/CD 117− cells. CEC subpopulation analysis showed CD109 were also enumerated. No severe side-effect was observed during treatment. The first MRI, 2 months after treatment onset,
P.077*. CANCER STEM CELLS IN GLIOBLASTOMA, WHAT ARE THEY? A. Golebiewska1, N. H. Brons2, R. Bjerkvig1,3, and S. P. Niclou1; 1Norlux Neuro-Oncology Laboratory, Public Research Centre for Health (CRP-Santé), Luxembourg, Luxembourg; 2Core Facility Flow Cytometry, Neuro-Oncology Laboratory, Public Research Centre for Health (CRP-Santé), Luxembourg, Luxembourg; 3Norlux Neuro-Oncology Laboratory, Department of Biomedicine, University of Bergen, Bergen, Norway

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

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

The efficacy of small molecule kinase inhibitors has recently changed standard clinical practice for several solid cancers. Glioblastoma is a solid cancer that universally recurs and unrelentingly results in death despite maximal surgery and radiotherapy with concomitant and adjuvant temozolomide. Several clinical studies using kinase inhibitors in glioblastoma have been reported. The present study systematically reviews the efficacy, toxicity, and tissue analysis of small molecule kinase inhibitors in adult patients with glioblastoma as reported in published clinical studies and determines which kinases have been targeted by the inhibitors used in these studies. Publications were retrieved using a MEDLINE search and by screening of meeting abstracts. A total of 60 studies qualified for inclusion, 25 of which were phase III studies. 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, PKCβ, and PDGFR).

P.079. NPAS3 IS A NOVEL LATE-STAGE ACTING PROGRESSION FACTOR IN GLIOMAS WITH TUMOR SUPPRESSIVE GENES N. Ajeung1, M. Rana2, P. Gould2, and D. Kamnasaran1; 1Department of Pediatrics, Centre de Recherche du CHUL & Laval University, Quebec, QC, Canada; 2Department of Pathology, Laval University, Quebec, QC, Canada

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

P.080. A NOVEL METHOD TO ENRICH FOR GLIOMA STEM CELLS FROM GLIOMA CELL LINES N. Ajeung1, M. Rana, and D. Kamnasaran; Department of Pediatrics, Centre de Recherche du CHUL & Laval University, Quebec, QC, Canada

BACKGROUND: Glioma stem cells (GSCs) are inherently similar to stem cells except they can transform into tumors reminiscent of the pathological features of the originated tumor mass. GSCs serve as an excellent pre-clinical model to comprehend tumor re-growth and treatment resistance. Several approaches were previously described to purify GSCs, but seemingly appeared to be laborious, costly, and sometimes with poor yield. Our objective was to investigate alternative strategies to cost-effectively and efficiently enrich for GSCs. METHODS AND RESULTS: We grew 3 glioma cell lines in a serum-free / 10% FCS, tumorsphere differentiation occurred. In addition, the tumorspheres can transform in vitro and with the ability to grow into tumors having similar pathological hallmarks but faster growth in comparison with xenograft tumors derived from the growth of glioma cell lines. These findings were overall similar with passages 1, 10, and 30 GSCs examined. CONCLUSIONS: We have discovered an alternative strategy to enrich for glioma stem cells from glioma cell lines in a cost-effective, easy, and efficient manner. Current efforts are undertaken to utilize our protocol to enrich for glioma stem cells from surgical tissues.

P.081. A CHEMICAL GENETICS SCREEN IDENTIFIES NOVEL STEROID INHIBITOR DRUGS THAT INHIBIT THE GROWTH OF GLIOMA CELL LINES N. Ajeung1, M. Rana1, D. Poirier2, and D. Kamnasaran1; 1Department of Pediatrics, Centre de Recherche du CHUL & Laval University, Quebec, QC, Canada; 2Laboratory of Medical Chemistry, Oncology and Molecular Endocrinology, Centre de recherche du CHUL & Laval University, Quebec, QC, Canada

BACKGROUND: Gliomas are among the top 5 causes of cancer-related deaths, representing about ~60% of the cases in adults and ~30% in children. Despite current treatments (surgery, radiation, and chemotherapy), the
overall survival is still poor. Current promises exist with patients treated with adjuvant temozolomide; however, only 10%–15% typically have a positive response with combined surgery and radiation therapies leading to prolonged survival of up to 2 years. Since a wide range of steroid receptors are expressed in gliomas, our objective was to investigate whether novel classes of steroid inhibitor drugs can be used efficiently to inhibit glioma growth. To achieve this, we studied the effect of these drugs on the growth of glioma 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 cancer cells (n = 5/5) within a 24-hour period and with a normal human astrocyte cell line. 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.082. A CHEMICAL GENETICS SCREEN IDENTIFIES NOVEL STEROID INHIBITOR DRUGS THAT INHIBIT THE GROWTH OF GLIOMA STEM CELLS

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BACKGROUND: Glioma stem cells represent a fraction of cells within a tumor mass that are postulated to be responsible for tumor re-growth. Moreover, recent studies have associated glioma stem cells with impeccable chemoresistance mechanisms, leading to an overall poor survival and failure among patients treated by conventional adjuvant chemotherapy. Since a wide range of steroid receptors are expressed in gliomas, our objective was to investigate whether novel classes of steroid inhibitor drugs can be used efficiently to inhibit glioma growth. To achieve this, we studied the effect of these drugs on the growth of glioma stem cells. METHODS AND RESULTS: We screened using a candidate chemical structure approach, a library of 400 steroid inhibitor drugs on 5 human glioma stem 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 24 hour period, and with some death of normal human neuro-progenitor cells. These drugs induced significant apoptosis, resulting in an overall decreased viability and proliferation of the cells in a dose-dependent manner (5 and 10 μM). Furthermore, significant inhibition of transformation was noted. CONCLUSIONS: We have discovered a novel chemically distinct class of drugs that can significantly inhibit the growth of glioma stem cells. Current efforts are undertaken to study more of the mechanistic function of these drugs.

P.083. BRAINSTEM GLIOMA IN ADULTS: A RETROSPECTIVE STUDY

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INTRODUCTION: Brainstem glioma are rare in adults. Literature on the subject is limited to small retrospective studies that described natural course, clinical-radiological presentation, and prognostic factors. Need for histopathological confirmation and therapeutic planning remains controversial. Surgery is first choice when tumor site permits it, even when only subtotal resection can be reached. Nevertheless, radiotherapy is very useful when tumor site is not easily accessible and for patients with poor clinical condition. Radiotherapy is better tolerated 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-molecular 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 cromal 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 treated 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.084. GAMMA-KNIFE RADIOSURGERY FOR RECURRENT GliOBLASTOMA RESISTANCE TO THE TEMOZOMOLIDE

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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. Gamma-knife radiosurgery (GK) stereotactic radiosurgery is a safe and less invasive treatment used as adjuvant therapy for patients with glioblastoma. Several studies have yielded conflicting results in the effectiveness of radiosurgery in glioblastoma. This article describes the results of our institutional experience with GK adjuvant therapy in the treatment of patients with recurrent glioblastoma resistance to the temozolomide. MATERIALS: 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 18 Gy (range: 15–20 Gy) prescribed to the 50% (range: 45%–80%) isodose line that encompassed the target volume. The median follow-up time was 22.5 months (range: 14–37 months). RESULTS: Median survival time of patients treated with GK was 19.0 months and without GK was 15.0 months. Treatment was well tolerated by all patients. No acute toxicities CTCAE Grade II occurred. Median survival time of patients treated with GK was 19.0 months and without GK was 15.0 months. CONCLUSIONS: GK radiosurgery is a relative safe and less invasive treatment and may play an important role in the treatment of recurrent glioblastoma resistance to the temozolomide.

P.085. DOES GENDER MATTER IN GliOBLASTOMA?

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

Abstracts
Variables analyzed were age, gender, clinical presentation, pre- and postsurgery 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 = 0.3; age, median age 56 years (treatment) vs 64 years (no treatment), P < 0.001; initial KPS score 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 < 0.001. 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 < 0.001) were independent predictors of no treatment after surgery. We analyzed why there were more women in the nontreatment group. Women in the whole series were older than 60 years, P = 0.1, they had a worse KPS before, P = 0.4, 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 = 125) 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: 55 patients with glioblastoma (4 males and 2 females; median age 31 years) which was treated with recurrent spinal cord glioblastoma were treated with bevacizumab (10 mg/kg given once every 2 weeks where 2 treatments constituted a cycle of therapy). All patients had failed surgery and temozolomide-based chemoradiotherapy and post-radiotherapy temozolomide. Blood counts, chemistry panel, urine protein to creatinine ration, and neurologic examination were obtained bi-weekly. Contrast-enhanced spine MRI was performed after 1 cycle of therapy and thereafter following every 2 cycles of bevacizumab. RESULTS: Treatment-related complications included fatigue in 6 patients, constipation in 4, hypertension in 2, thrombophlebitis in 2, and infection without neutropenia in 2. There were 3 grade 3 toxicities (1 each fatigue, leukopenia, and thrombophlebitis). There were no treatment-related deaths. After one cycle of bevacizumab, 1 patient (17%) demonstrated progressive disease, 2 (34%) partial responses, and 1 (51%) stable disease. Overall median response or stable disease duration (disease free progression) was 7 months (range: 3–11 months). Overall median survival was 9 months (range: 5–13 months). CONCLUSIONS: Bevacizumab was well tolerated, has tolerable toxicity, and apparent activity in this small cohort of adults with recurrent spinal cord glioblastoma.

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

P.088. CONCURRENT RADIOTHERAPY–FOTEMUSTINE COMBINATION FOR NEWLY MALIGNANT GLIOMA PATIENTS: A PHASE II TRIAL
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PURPOSE: Fotemustine is a nitrosourea compound used for the treatment of malignant gliomas, especially in France. Recently, an EORTC-NCIC study has shown that a concomitant combination of radiotherapy plus temozolomide (an oral cytotoxic drug) improved survival in glioblastoma patients. We set out to test a concurrent combination of radiotherapy and fotemustine for newly malignant gliomas. METHODS: A prospective single-centre phase II study opened for accrual in September 2004. Patients over 18 years of age able to give informed consent and with histological proven, newly diagnosed supratentorial malignant gliomas were eligible. All patients were treated by a standard cranial irradiation (conformal irradiation, tumor bulk plus a margin of 2.5 cm) and concomitant daily administration of 10 mg/m2 of fotemustine (5 days per week, 6 weeks, 1 hour 30 minutes before 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 stereotactic biopsy. The concurrent radiotherapy–fotemustine combination was well tolerated: toxicity was mild and 3 hematologic toxicities grade 3–4 were observed. Median survival from initial diagnosis was 9.9 months, 2 patients are currently alive. Median survival was 11 months for surgery and 9 months for stereotactic biopsy. CONCLUSIONS: Concomitant radiotherapy–fotemustine combination is safe and well tolerated. Overall survival of over 10 months for the whole population compares favorably with other reports.

P.089. GENE EXPRESSION PROFILING PREDICTS RESPONSE TO TMZ IN GLIOBLASTOMAS IN VITRO
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Glioblastomas are highly lethal neoplasms that cannot be cured which currently available therapies. Temozolomide (TMZ) is a recently introduced alkylating agent that has yielded significant benefits and become a key agent in the treatment of high grade gliomas including glioblastoma. However, its survival benefit remains unsatisfactory. Understanding the molecular basis of TMZ sensitivity/resistance is necessary for improving the treatment outcome by devising strategies that are able to circumvent primary drug resistance. We therefore combined the in vitro TMZ response with microarray gene expression data to identify genes that could potentially be used to predict the response of glioblastomas to TMZ in vitro.
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 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 has several limitations, our report identifies genes which may be 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-DD) in patients with recurrent glioblastoma (GBM). In patients with relapsed GBM, dose-dense regimens of TMZ (TMZ-DD) have been applied and the weekly alternating showed low toxicity and good efficacy. METHODS: We have retrospectively analyzed clinical data of 14 patients treated with TMZ-DD 150 mg/m² 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 undergoing TMZ-DD. We analyzed the evidence of progression and/or neurosurgical progres- sion 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 concomitant chemoradiotherapy (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%) were not submitted to RT for the extension of the disease (both frontal lobes). All patients were operated, or as primary treatments, 8 patients were submitted to TMZ-SS: median number of cycles delivered was 4 (range: 2–12 cycles). At clinical and/or neuroradiological progression, all patients underwent TMZ-DD: 12 after the first progression (85.7%) and 2 patients (14.3%) for progressive disease 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 (20%) were unmethylated and 3 patients were methylated (50%). One patient achieved the resectability after 3 months of TMZ-DD. Median progression free survival was 3.6 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 investigate.

**P.091. HYPERFRACTIONATED 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 hyperfractionated high-dose irradiation planned by MET-PET with GBM patient MRI, PET, and MGMT. MATERIAL AND METHODS: Thirty-nine postoperative patients with GBM were treated by IMRT using the tomotherapy system with concurrent chemotherapy. The gross target volumes by MRI (GTV-MRI) and GTV-MET, and CTV was defined as the area including the total volume of GTV-MRI and GTV-MET, and CTV was defined as the area including the total volume of CTV-MRI and CTV-MET. The GTV and CTV were expanded uniformly by 0.5 and 0.2 cm to generate planning target volumes, PTV-1 and PTV-2, respectively. IMRT was performed in 8 fractions, planning the dose for PTV-1 at 56 Gy and PTV-2 at 40 Gy with concurrent chemotherapy by temozolomide (TMZ) of 75 mg/m² daily. Adjuvant chemotherapy by TMZ of 150 mg/m² was repeated every 4 weeks. At a median follow-up of 13 months, the treatment outcomes and toxicity were evaluated. RESULTS: The median survival time was 18.5 months. The 1- and 2-year progression-free survival rates were 59% and 20%, respectively. The 1- and 2-year overall survival rates were 74% and 24%, respectively. The high incidence of CSF dissemination was demonstrated as the pattern of recurrence, while the incidence of local recurrence was relatively low. Five patients experienced acute grade 1 toxicity during the treatment. Nine patients experienced grade 2 toxicity, including radiation necrosis, cerebropathy, and intratumoral hemorrhage. CONCLUSIONS: Our regimen of IMRT with TMZ using MET-PET contributed to the control of residual infiltrating tumor, resulting in better survi- val of GBM patients. Survival times in this pilot study are encouraging, and relative favorable result might be from the decreasing of local failure, which suggested that original lesion could be well controlled by high-dose radiation planned by MET-PET. On the other hand, radiation-induced late toxicity was the next problem.

**P.092. EFFICACY AND TOLERABILITY OF LEVETIRACETAM MONOTHERAPY IN PATIENTS WITH PRIMARY BRAIN TUMORS AND EPILEPSY**

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**OBJECTIVES:** Epilepsy is a common symptom in patients with brain tumors, particularly gliomas. Enzyme-inducing or -inhibiting antiepileptic drugs (AEDs) are known to interact with antineoplastic drugs and corticos- teroids, 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 ongoing to the routine care of patients with brain tumors. RESULTS: Three patients 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 the period before surgery. Seven patients (18%) had to switch to another AED because of lack of efficacy (n = 4) or adverse effects (n = 3). Efficacy was not related to any clinical characteristic. CONCLUSIONS: Although earlier studies indicate that add-on therapy with levetiracetam seems effective, there is hardly
any information available on levetiracetam monotherapy. Our results indicate that levetiracetam monotherapy is efficacious in reducing seizures and is well tolerated in the majority of glioma patients suffering from epilepsy.

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

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PURPOSE/OBJECTIVES: 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 surgery, chemotherapy, and radiation 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 (N = 206). 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) (1.8 months for KPS ≤50 vs 17.2 months for KPS = 90–100, P < .001); age at diagnosis (5.1 months for age 70–79 vs 31 months for age 80 or greater, P < .001); the extent of disease with patients with bilateral disease (P = .003), multifocal disease (P = .02), and multicentric disease (P = .002) doing worse in all cases. Patients treated with radiation had longer OS of 6.7 vs 1.9 months for those not treated with radiation (P < .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 < .001). On multivariate analysis, higher KPS (P = .006), surgical resection (P < .001), radiation (P < .001), and chemotherapy (P < .001) were all found to be independently associated with improved OS. CONCLUSIONS: These data suggest that aggressive treatment with radiation, chemotherapy, and radiation 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 carcinogenesis, 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 IIIb study. These studies were performed in adult patients with recurrent or refractory HGG (AA, WHO grade III and GBM, WHO grade IV). Trabedersen was administered intratumorally by convection-enhanced delivery. RESULTS: In the phase IIIb study, a total of 143 patients were randomized to either 1 of the 2 doses of trabedersen (10 or 80 μM) to chemotherapy (TMZ or PCV). One hundred and thirty-four patients (AA = 39; GBM = 95) received study medication during a treatment period of about 6 months. In the entire study population, the 10-μM trabedersen group had the highest tumor control rate (CR + PR + SD) at 14 months (22.5% for 10 μM trabedersen vs 6.7% for chemotherapy). The highest efficacy was observed in AA patients treated with 10 μM trabedersen (no proportion of patients showing a response (either CR or PR) 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 SAPPHIRE in patients with recurrent/ refractory AA was started. Patient recruitment is ongoing. Primary endpoint is 2-year survival; secondary endpoints include overall survival, tumor response, quality of life, and safety.

P.095. INCIDENCE AND SURVIVAL IN GLIOBLASTOMA PATIENTS WITH PSEUDO-PROGRESSION IN A SINGLE INSTITUTION

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We evaluate incidence and impact in survival and progression-free survival of pseudo-progression (PSP) in patients with glioblastoma (GBM). From December 2006 to September 2009, 61 primary GBM were treated in our institution with resection (54) or biopsy (7) followed by TMZ radiotherapy followed by TMZ (150–200 mg/m²/day for 5 days each 28) for 2 years or until disease progression or unacceptable toxicity. One month afterchemo-adoion, 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 years (range 18–72), 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 33 patients (53.5%) and stable disease or minor partial response in 26. All continued with 2 or 3 cycles of temozolomide. Of the 35 patients with progression in the postraadiotherapy, MRI 14 (22.9%) had PSP and 21 (34.4%) real early progression (REP). Fifteen of 21 patients (71%) with REP developed new clinical symptoms during or 1 month after radiotherapy but only 4 of the 14 patients (28%) with PSP had new symptoms during this period. PFS was 37% and 21% at 12 and 24 months, respectively; the 12 and 24 months survival rate was 59% and 43%, respectively. There was a statistically significant difference in PFS in patients with PSP (P < .0013) and a trend toward better overall survival for patients with PSP but it did not reach statistical significance (P = .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 parameters that distinguish between REP and PSP.

P.096. SALVAGE THERAPY AFTER FAILURE OF FIRST LINE TREATMENT FOR GliOBLASTOMA Multiforme

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Concomitant chemoradiotherapy is a 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 226 patients until the end of 2008. Of those 94 had radiologically demonstrated disease progress 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 bevacinabum and irinotecan). Overall median survival was 16.6 (SD 1) weeks, in patients receiving best-supportive care it was 7.1 (SD 3.3) weeks, 13.5 weeks in patients re-challenged with temozolomide, 26.5 (SD 7.9) weeks in patients which were operated and later received systemic therapy,
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 parametern maps for V_Ktrans, V_eff, and V_Area. Region of interest (ROI) placed by the radiologist 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 with 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/Tmx a clear decrease in Ktrans and V_Area could be seen after only 3 weeks of treatment with DCE–MRI, indicating a decrease of vascular permeability and leakage respectively.

CONCLUSIONS: Important surrogate markers for angiogenesis, diffusion, and cell density tend to assume a more “normal” pattern after a very short treatment period in a series of patients. Studies with the objective to expand the number of patients and correlate these findings to patient outcome are ongoing at our department.
In total, 32 cycles of chemotherapy were applied. The combination was
followed by low-dose weekly CCNU after failure of dose-dense temozolomide alone.
Hematotoxicity, though, has to be controlled vigorously. The results have to be
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 tumor resection and performed an aimed coagulation without traumatization of eloquent cortex. CONCLUSIONS: The gross total resections of anaplastic gliomas could be performed in eloquent brain regions with an acceptable level of motor and speech impairment. The improved preoperative planning and image-guided tumor thermodestruction allow maximal safe resection of tumor that predict higher levels of quality of life in patients with brain gliomas in eloquent area.

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

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 thrombopenia, and 1 patient had asymptomatic leucopenia. But only 1 patient out of the 10 included in this arm had to stop TMZ because of hematotoxicity. 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 treatment.

CONCLUSION: Hematoxicities are very 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 transcription, 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 chemotherapeutic responsiveness and to clarify underlying molecular mechanisms. MVP and MVP–GFP fusion proteins were overexpressed by plasmids and adenoviral constructs. Endogenous MVP expression was repressed by shRNA. Protein expressions were detected by immunofluorescence and Western blot. Consequences of MVP modulation on cell proliferation, migration, and invasion capacities were analyzed by growth curves, scratch and transwell-chamber assay, respectively. Moreover, tumor formation in dependence of MVP expression was tested in SCID mice. Ectopic MVP expression in MVP-negative H7 glioma cells led to a significantly enhanced proliferative and migratory potential in vitro. Especially responsiveness to epidermal growth factor (EGF)-mediated growth stimulation was increased parallelly by significant upregulation of MAPK and PI3K pathway indicated by phosphorylation of ERK and AKT, respectively. Accordingly, several signal mediators of these pathways, including PTEN and P66, were detected in immunoprecipitates from MVP-overexpressing cell clones. MVP transgenic cells were significantly resistant to cell death induced by serum-starvation but only marginally protected against the cytotoxic effects of diverse chemotherapeutics. Expression of a truncated MVP molecule harboring only the MVP coiled-domain and/or MVP down-modulation by shRNA in MVP-positive GBM cells induced programmed cell death and a high hypoxia resistance to a pro-apoptotic factor starvation. Tumor growth in SCID mice was significantly enhanced in all MVP overexpressing H7 subclones when compared with vector controls. Our data prove a significant contribution of vaults/MVP to the malignant phenotype of human GBM cells supporting activation of oncogenic signaling pathways and growth/survival factor responsiveness.

P.106. A FIVE-YEAR FOLLOW-UP EXPERIENCE IN NEWLY DIAGNOSED Glioblastoma AND comcomitant photographed: TOLERANCE, COMPLIANCE, EFFECTIVENESS, AND SECOND-LINE THERAPIES

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Since 2005 the Stupp protocol with concomitant regimen of chemoradiotherapy followed by monthly adjuvant cycles of temozolomide has become the standard first-line approach in newly diagnosed glioblastoma after surgery. In this study, we present a 5-year follow-up experience in newly diagnosed glioblastoma treated with the concomitant protocol at the Neurosurgery Units of Policlinico and Galeazzi Institutes. From January 2003 to December 2009, we enrolled 91 patients eligible to complete the concomitant phase. We excluded patients in poor general or neurological conditions who needed a rehabilitation period prior to be submitted to radiotherapy. People over 70 years old were addressed to a modified protocol with a reduced dosage of radiotherapy, except for 3 patients in very excellent conditions who were submitted to standard protocol. There were 38 women and 53 men ranging from 18 to 75 years. All of them were submitted to gross total removal of the lesion (as assessed by postoperative gadolinium-enhanced CT or MRI scan) except for 6 deep-seated lesions, submitted to stereotactic biopsy. In 63 cases, MGMT status was analyzed. All the patients were able to finish the concomitant phase of the protocol. In 4 cases a reduced dose of temozolomide was administered because of the onset of pias- trinopoeia. In the adjuvant phase, we preferred to administer 12 monthly cycles of temozolomide instead of the standard 6 months regimen. In the majority of patients (90%), we adopted a modified schedule (150 mg/day 1-5, 75 mg/day 6–10 day). Four patients experienced a bronchoeupeumonia, 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 Gladel wafers were placed in the cavity), and 80% of the patients with recurrence received a second-line therapy: rechall- enge of temozolomide (the 1-week on–one week off regimen in unmethylated tumors), fotoomustine, 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.
Objective: The influence of early start of radiotherapy plus concomitant and adjuvant temozolomide on overall survival (OS) in GBM patients was retrospectively investigated. METHODS: Forty-eight consecutively verified glioblastoma patients (median age 62.5 years, from 25 to 82, 19 females and 29 males, WHO performance status 0–1) received surgery (15 biopsy, 18 partial, and 14 complete resections) and radiotherapy (start median 17.5 days, from 12 to 27 days after surgery) with concomitant and adjuvant TMZ (all patients completed 60 Gy in 2 Gy/day fractions, 5 day/week, 40 of 60completedconcomitantTMZ,18of40additionally6cyclesofadjuvantTMZ).Nosignificantcomplicationsleadingtorevision surgeryoccurred. RESULTS: Altogether, the 12 of 24 month OS was 54/20.2% with a median survival of 13.7 month. 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 28.8/5.5%, with 7.7-month median survival (Log-rank, P = 0.005). The OS comparing RT start <16days with >16days was not significantly different. Extent of surgery influenced OS in the young age group (biopsy vs complete: P = 0.06), but not in patients (>65 years (P = 0.5). CONCLUSION: As the 12 of 24-month OS in our patients (65% median survival at 7 years) was higher than the OS of the EORTC study (61.1/26.5%) with comparable demographics except for therapy start (EORTC median 3 weeks), we speculate that early start of the RT/TMZ might be of additional benefit.

P.110. PHASE II STUDY OF IFOFASAMIDE, 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 prolonged a patient’s good quality of life. METHODS: This trial was an open-label, single-center Phase II study. Forty-two patients with a first GBM relapse after surgery followed by standard radiotherapy (60 Gy) was an open-label, single-center Phase II study. Forty-two patients with a first GBM relapse after surgery followed by standard radiotherapy (60 Gy) were eligible for participation. The primary endpoint was progression-free survival (PFS) at 6 months after the ICE treatment (PFS-6), and secondary endpoints were response rate, toxicity, and overall survival. Chemotherapy consisted of ifosfamide (1000 mg/m² on Days 1, 2, and 3), carboplatin (110 mg/m² on Day 1), and 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 9–43%). Adverse events were frequently observed: mostly neutropenia and thrombocytopenia. CONCLUSIONS: This regimen was well tolerated and has some activity and could be one of the options for patients with recurrent GBM.

P.111. LONG-TERM SURVIVORS OF GLIOBLASTOMA

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There is no generally accepted definition of long-term GBM survivors (LTGBMs). Usually, most authors define long-term GBM survivor as a patient who survives at least 3 years after the histological diagnosis of glioblastoma. LTGBMs are uncommon and are reported to occur in 0.5–16% of cases. In our ENOK (Ege University Neuro-Oncology Council) cases we have 12 of 372 GBM patients who survived more than 3 years (3.2%). The clinical and molecular factors that contribute to long-term survival are still unknown. Authors underline the association of glioblastoma long-term survival with prognostically favorable clinical factors, in particular young age and good initial performance score (KPS) as well as MGMT promoter hypermethylation.

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

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Glioblastoma multiforme (GBM) is the most common form of malignant brain cancer in adults. Patients with GBM have a uniformly poor prognosis, with a median survival of 1 year thus, advances on all scientific and clinical fronts are needed. We have developed a human glioblastoma xenograft model in nude rodents that is characterized by a highly infiltrative nonangiogenic phenotype. Upon serial transplantation, this phenotype will develop into a highly angiogenic tumor. Thus, we have developed an animal model where we are able to establish two characteristic tumor phenotypes that define glioblastoma (ie, diffuse infiltration and high neovascularization). It is well established that the cancer genome is molded by the dual processes of somatic mutation and selection. In order to assess whether the observed phenotypic shift is because of clonal selection in vivo, we have performed high-resolution aCGH on primary tumors and xenografts derived thereof. We show that although the overall genomic pattern is highly conserved, additional genomic events trigger the switch from an invasive to a highly angiogenic phenotype observed in vivo. We are currently further analyzing our findings by applying whole exome sequencing to the analyzed samples to delineate the mutational evolution of xenografted gliomas at single-nucleotide resolution and identify new mutational events linked to the phenotypic switch. This molecular dissection of the 2 hallmarks of GBM could lead to the identification of potential biomarkers that may facilitate the elucidation of the molecular pathways involved in the switch from invasive to angiogenic growth, thereby potentially opening new diagnostic and treatment avenues in the clinic.

P.113. THROMBOCYTOPENIA IN GLIOBLASTOMA PATIENTS TREATED WITH ANTIPELTIC DRUGS AND RADIO-CHEMOTHERAPY BASED ON STANDARD REGIMEN

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INTRODUCTION: Seizures in brain tumor patients are a common event. Tumor epilepsy 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). The high frequency of thrombopenia because of temozolomide (TMZ) is frequent; 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 institution database. national database, 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 operationalized 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 < 0.01), age (P < 0.001) and VPA (P = 0.004). Platelet count < 100 × 10^9/L was only associated with TMZ dose (P = 0.01). Age (P = 0.07) and VPA (P = 0.12) 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 thrombocytopenia. Although VPA and age were main determinant factors of thrombocytopenia. Although VPA and age were main determinant factors of thrombocytopenia.
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+/TELOMERASELOW PROGENITOR CELLS IN GLIOBLASTOMA-DERIVED CANCER STEM STELL LINES
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Glioblastoma multiforme (GBM) is paradigmatic for the investigation of cancer stem cells (CSC) in solid tumors. The CSC hypothesis implies that tumors are maintained by a rare subpopulation of CSC that gives rise to rapidly proliferating progenitor cells. Although the presence of progenitor cells is crucial for the CSC hypothesis, progenitor cells derived from GBM CSC are yet uncharacterized. Our data suggest that in the subgroup of CD133+ primary astrocytic GBM, CD133+ /telomerase+ CSC give rise to non-tumorigenic, CD133+ /telomerase– progenitor cells. The progenitor cell population proliferates rapidly resulting in significant telomere shortening when compared with the CD133+ compartment comprising CSC. The average difference in telomere length as determined by a modified multi-color flow FISH (fluorescence in situ hybridization) was 180 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 4 Belgian university hospitals. Tumor response and anti-edema effect were assessed by magnetic resonance imaging (MRI, including T1-weighted contrast enhanced images (according to recently modified Macdonald’s criteria). Primary end-point was PFS, secondary endpoints were response rate, overall survival, and safety.

RESULTS: The 6-month PFS was 32% and median survival time was 6.7 months. The overall response rate was 43.4%, with 4.3% 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 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 therapy an attractive approach in the management of GBM. Our group is currently active in identifying and characterizing novel biomarkers and therapeutic targets involved in the angiogenic switch observed in malignant gliomas. Making use of a clinically highly relevant xenograft model that recapitulates the invasive and angiogenic properties of GBM within consecutive generations of rats, we have previously performed a large-scale iTRAQ-based proteomics study comparing nonangiogenic to angiogenic GBM phenotypes. From more than a thousand quantifiable proteins identified in membrane fractions, about 150 proteins showed increased expression in angiogenic gliomas. 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 GLIOBLASTOMA: A PHASE II MULTICENTER ITALIAN STUDY
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BACKGROUND: Recent evidence indicates that antiangiogenic therapies have an important role in recurrent high-grade gliomas. Bevacizumab, a humanized monoclonal antibody against vascular endothelial growth factor (VEGF), has been reported to be active with acceptable toxicity. We report the preliminary results of a multicenter 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. The overall response rate was 43.4%, with 4.3% 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 in this series derived a durable treatment effect with evidence for a metabolic response in addition to an edema reducing effect.
patients. Forty percent of responders had unmethylated MGMT promoter. The most frequent side effects were: hematological grade 3–4 toxicity (21%); fatigue (46%); mild arterial hypertension (9%); and one grade III hypertension with reversible hypertensive encephalopathy; hemorrhagic events (12.5%) (2 lobar hemorhrs, 2 asymptomatic intracranial bleedings, 1 esophageal bleeding); thrombotic events (9%) (one pulmonary embo- lism, 2 TVP, and 1 stroke); mild proteinuria (14%). CONCLUSIONS: Bevacizumab in combination with fotemustine was well tolerated and active in recurrent glioblastoma. The correlations between MGMT status, MRI perfusion, and response is ongoing.

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

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INTRODUCTION: Glioblastoma multiforme is the commonest primary malignant brain tumor in adults, and is usually rapidly fatal. Until 2004, standard treatment in the UK comprised 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 temozolo- mide 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

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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 progress (PD) 5 weeks after treatment start. Regarding anaplastic astrocytomas, 4 (of 6) patients showed SD for a time period of 2–9 months. Partial response in 2 patients was lasting for 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-food syndrome grade II–IV. One gastrointestinal bleeding was reported, but no origin of hemorrhage was found. Some patients reported episodes of diarrhea which in one case lead to treatment discontinuation. Deep venous thrombosis was not observed in our patient cohort. CONCLUSION: Multikinase inhibitor sorafenib showed responses in heavily pretreated patients with recurrent CNS tumors.

P.120. ACTIVATION OF P53 BY MDM2 ANTAGONISTS DOWN-REGULATES SURVIVIN AND INDUCES CELL-CYCLE ARREST AND APOPTOSIS IN HUMAN GLOBLASTOMA MULTIFORME

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

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

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The founded relevance of surgical removal in the combined therapeutic strategy of malignant gliomas and the opportunity offered in the last few years by new unconventional treatments or second-line chemotherapeutic schedules have deeply modified the indications to surgical treatment of progressive and recurrent malignant gliomas. In the last 2 years, we have oper- ated 22 recurrent malignant gliomas (12 glioblastoma, 7 anaplastic oligodendroglioma, and 3 anaplastic astrocytoma). At the moment of the initial diagnosis, all the patients have been submitted to first-line surgical treatment, radiotherapy, and chemotherapy with temozolomide, and/or 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 wafers were positioned into the resection cavity. The main early compli- cations of second surgical treatment have been local, as CSF fistula and wound dehiscence (4 cases), and were observed during the immediate postoperative period. Only in one case of temporal GBM, the second surgical resection was followed by an early progressive neurological deterioration, and the patient died 3 months after. The patients, followed in our depart- ment, with the relevant contribution of our home assistance service, have been submitted to second and/or third line chemotherapy; in 4 cases a highly used streptokinase radiotherapy has also been performed. 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 patients’ setting with more specific indication at second surgical removal.

LOW-GRADE GLIOMAS

The clinical course of grade II gliomas remains variable and their transformation into a more malignant phenotype is highly unpredictable. There have been attempts to identify biological markers that can facilitate prediction of prognosis in individual cases of low-grade astrocytomas, but so far without much success. PROX1 is a transcription factor that plays a critical role in the development of various organs and that has been ascribed both oncogenic and tumor suppressive functions in human cancers. In a recent study, we have shown that PROX1 may act as a diagnostic marker for high-grade astrocytic gliomas. The aim of this study was to address the prognostic role 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.124. PROX1 IS A PREDICTOR OF SURVIVAL FOR ASTROCYTIC GLIOMAS BUT NOT FOR OLIGODENDROGLIOMAS GRADE II

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BACKGROUND: Pleomorphic granular cell astrocytoma in the pineal region is exceedingly rare, and its clinicopathological features are distinctive. CASE REPORT: A 67-year-old woman was admitted with a staggering gait. Magnetic resonance imaging revealed a mass lesion at the pineal gland accompanied by obstructive hydrocephalus. Following surgery, pathological examinations demonstrated a pleomorphic granular cell astrocytoma. The patient has been free from recurrence for 24 months after surgery without adjuvant therapy. PATHOLOGICAL FINDINGS: The specimen exhibited nuclear and cytoplasmic pleomorphism. The nuclei varied in size, shape, and coarseness. Variability was also observed in the eosinophilic granular bodies, Rosenthal fibers, and spindle-shaped tumor cells. GFAP, S-100, and vimentin were immunohistochemically positive. Reticulin work in tumor between the tumour cells, granular and balloonated
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 World Health Organization (WHO) grade II gliomas. PATIENTS AND METHODS: We selected patients treated by tmz and then by surgery for a WHO grade II glioma, from the database of two French centers (Montpellier and Nancy). Usual oncological data were collected. Patients benefited, 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 surgery. The presence of a gadolinium enhancement was systematically analyzed. RESULTS: Twelve patients with a median age at diagnosis of 40.5 years (22–51) and at assessment of 48 years (26–55.5) were selected. The median follow-up was 64 months (31.5–120) and the median time between assessment and the last surgery was 20.5 months (3–70). Symptoms at diagnosis were partial seizures in 4 (33.5%) cases and were generalized seizures in 8 (66.5%). Tumor location was frontal in 6 cases (3 right and 3 left), fronto-temporal in 4 cases (1 right, 3 left), and left temporal in 2 cases. Tmt alone has been prescribed for 11 patients and tmz + fotemustine for 1 patient. Clinical and radiological evaluation after chemotherapy will be detailed. Seven patients had one functional surgery, 3 had two procedures, and 2 had three procedures. Pre and postoperating volume will be clarified. After the last surgical procedure, 10 (83%) patients had a WHO grade II oligodendroglioma (4 with some anaplastic foc.) 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.128. COMPARATIVE ANALYSIS OF IDH1 MUTATION, TP53 MUTATION, AND MGMT HYMЕРМЕTHYLAΤION IN ASTROCYTOMAS

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Abstracts

TP53: mutation, MGMT hypermethylation and, more recently, IDH1 mutations have been identified as precocious genetic aberrations in gliomas, but their mutual relationships during glioma formation have not been clarified. We performed a comparative genetic analysis in a selected group of 18 patients affected by low-grade astrocytomas and in these same patients at tumor recurrence, irrespective of anaplastic progression. The aim of the study was to investigate the natural history of disease, excluding the interference of radio-chemotherapeutic agents. MATERIALS AND METHODS: We studied 18 patients affected by fibrillary astrocytoma (9), gemistocytic astrocytoma (3), protoplasmic astrocytoma (6). They did not undergo radiotherapy or chemotherapy after first surgery. After a median follow-up of 72 months, 15 of 18 patients recurred and the tumor showed a more malignant phenotype. Three patients underwent a third surgical 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; IDH1 and TP53 mutations by sequencing analysis after PCR amplifications. RESULTS: Primary low-grade astrocytomas showed IDH1 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 IDH1 and TP53 mutations in primary tumors were confirmed. Furthermore, all losses of heterozygosity observed in the first sample were present also at recurrence. While IDH1 mutations were already present in all primary tumors but one, the MGMT and TP53 status changed 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 IDH1 toward accumulation of genetic aberrations was not investigated because of the small number of IDH1 wild-type patients at primary tumor. Finally, 5 patients out of 8 with MGMT hypermethylated and 8 of 10 with MGMT unmethylated at primary surgery acquired new losses of heterozygosity at recurrence. CONCLUSIONS: IDH1 mutation, MGMT hypermethylation, and TP53 mutations are precious events in astrocytomas. Our results confirm that IDH1 mutation is the earliest genetic aberration in these tumors and that is widely represented in low-grade astrocytomas. Interestingly, only tumors with unmethylated MGMT changed their methylation status becoming methylated.

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 caretaker 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 non-disclosure to others about the tumor diagnosis were also significant in the early illness experience. An important theme to emerge involved the patients describing what they perceived difficulties that 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.
PEDIATRIC BRAIN TUMORS

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

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Intrathecal chemotherapy is a crucial element in the treatment of 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 antiangiogenic chemother-apy. Since May 1998, patients received intrathecal 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. Intrathecal 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), meningism (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; diarrhea, n = 1). Since all patients received some sort of concurrent anti-cancer therapy, the efficacy of intrathecal therapy cannot be assessed independently. In conclusion, liposomal cytarabine alternating with etoposide appears to be feasible and well tolerated. Known side effects of liposomal cytarabine might occur less frequently if 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 (pinea l2 suprasellar) in Caucasians. Para axial tumors are mostly reported in Asian patients. Optic pathway germ cell tumors have been exceptionally reported. We report 3 of such cases in Caucasian patients. A 23-year-old male presented a diplopia with raised intracranial pressure, requiring ventriculostomy. The MRI showed a localized pineal tumor associated with raised seric hHCG (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 bulbo medullar 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 neuropathy. MRI showed a pineal region tumor. CSF HCG was raised (595 IU/L). This “biofoc” secreting tumor was treated according to GCT 96 SIOP protocol: chemotherapy (Etoposide ifosfamide and Carboplatin) followed by 54 Gy of hypofractioned 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 and at 3-years post standard and high-dose chemotherapy followed by a 24-Gy craniospinal irradiation with respectively a 1-, 2-, and 3-year follow-up. These cases emphasize the need of careful evaluation of optic pathway in patients with CNS germ cell tumors, both at time of diagnosis and relapse. Visual symptoms may be misleading when patients present with raised intra cranial pressure. Isolated involvement of optic pathway at diagnosis is a rare disease and requires a biopsy. Decreased vision after radiation therapy is not always because of radiation.

P.131. RESULTS OF TREATMENT RECURRENT HIGH-GRADE GLIOM (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 antiangiogenic therapy, bevacizumab, and a cytotoxic agent, irinote-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 14 patients (63.6%), the glioblastoma (GB) was histologically verified, and in 3 patients (13.7%) anaplastic astrocytoma (AA) was verified. Karnovsky was 50–100 (with median 80). All patients received 6-week cycles of combined therapy: bevacizumab 3 mg/kg on day 1, 15, and 29 days, with irinotecan 80 mg/m2 ×5 days every 2–6 weeks for a total of 306 courses (1–41 per patient) via an Ommaya reservoir. Intrathecal methotrexate and mafos-famide were additionally administered to 10 and 2 children, respectively. Known side effects of liposomal cytarabine might occur less frequently if the time intervals of treatment may be extended and bridged with etoposide.

P.132. OVERVIEW OF CHILDREN WITH ANAPLASTIC ASTROCYTOMA

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In conclusion, liposomal cytarabine alternating with etoposide appears to be feasible and well tolerated. Known side effects of liposomal cytarabine might occur less frequently if the time intervals of treatment may be extended and bridged with etoposide.

For the analyzed moment, 9 patients are still alive (40.9%), 13 died (59.1%); 1 patient with CR died in remission in 1.5 month after finishing therapy from leukoencephalopathy. The 18-month PFS in patients with GB was 0.11 and OS was 0.28. Objective response observed in 15 patients (78.9%); PR 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 leukoence-phantoma. Combination of bevacizumab and irinotecan is an effective in relapsed pediatric GB with acceptable toxicity. PFS in this group is higher than in patients with AA, what statistically proved (P = 0.5).

INTRODUCTION. Anaplastic astrocytoma (AA) is a rare tumor of CNS in children, which differs from the worse prognosis if only surgical treatment per-formed. MATERIALS AND METHODS: From 2000 to 2005 37 pts at the age from 5 months to 16 years (median 8 years) with the first time verified AA were observed. 4 patients received only resection, 8 pts - resection and radiotherapy (RT), 25 pts - complex treatment (combination of resection, RT and chemotherapy (CHT)). Total resection of a tumor performed in 15 pts, subtotal - in 7 pts, partial - in 12 pts, biopsy - in 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 ± 5% and 50 ± 9
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 meningioma at our Gamma Knife Unit during the period 1993–2009 was performed, particularly selecting 233 cases followed for more than 2 years.

MATERIALS AND METHODS: A retrospective review of 615 patients treated for single cranial base meningiomas, with an excellent preservation of neurological function and a significant improvement in the treatment of these meningiomas. The order of accumulating genetic aberrations has previously been described with the FISH technique, 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 aberrations 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) in 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.

MENINGIOMAS

P.134. CRANIAL BASE MENINGIOMAS: THE ESSENTIAL ROLE OF STEREOTACTIC RADIOGRAPHY
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INTRODUCTION: Surgical resection of cranial base meningiomas continues to present an enormous surgical challenge because of the complexity of the approaches and mainly of the possibility of disabling sequelae. In the past 2 decades, stereotactic radiosurgery has been advocated as the definitive treatment in the management of these tumors, as a first-line treatment or after incomplete resections, changing the current management protocols in the treatment of these meningiomas. MATERIALS AND METHODS: A retrospective review of 615 patients treated for single cranial base meningioma at our Gamma Knife Unit during the period 1993–2009 was performed, particularly selecting 233 cases followed for more than 2 years.

RESULTS: Two-thirds of the patients were females, with a global median age of 55 (25–84). The most frequent location was the cavernous sinus (37%), followed by clival and petroclival regions (16.3%). Forty-five percent of patients underwent radiosurgery. Additionally, the palpable cervical mass was radiosensitive. 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.

P.136. SURGICAL TREATMENT OF CENTRAL NERVOUS SYSTEM HEMANGIOPERICYTOMAS
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INTRODUCTION: Hemangiopericytomas (HPC) are rare, highly vascularized tumors derived from pericytial cells or Zimmerman’s pericytes, which tend to recur locally and metastasize extracranially. Treatment includes complete surgical resection followed by radiotherapy to optimize local recurrence control. We present our experience in the treatment of patients with HPC. MATERIALS AND METHODS: Retrospective analysis of clinical data from patients with HPC treated at the Department of Neurosurgery between June 1995 and February 2010 was reviewed to establish lesion location, associated symptoms, radiological features, preoperative embolization, intraoperative findings, postoperative complications, extent of resection, recurrences, and need for adjuvant radiotherapy. RESULTS: A total of 14 patients with HPC were subjected to surgery during this period, of which 9 were females (64%) and 5 males (36%). Mean age of patients in this series was 44 years (range 21–75), and mean follow-up duration was 50 months (range 7–147). Lesions were supratentorial in 7 patients (50%), infratentorial in 2 (14%), falco-tentorial in 2 (14%), skull base in 2 (14%), and dorsal spine 1 (8%). Headache was the most frequent symptom in 8 cases (57%) followed by neurological deficits in 7 (50%). Endovascular therapy was used in 5 patients (35%). Complete surgical resection was achieved in 11 patients (78%) and subtotal resection in 3 (22%). Eight patients received postoperative radiotherapy (57%). Recurrences were observed in 5 patients (35%), 4 at the primary site, and 1 at the craniospinal axis. Four of these patients were reoperated, and subsequently 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 aberrations 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) in 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. Therefore, a valuable criterion for the neurosurgeon’s postoperative management protocol.
P.138. IMPROVED PREDICTION OF TUMOR RECURRENCE 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 treated with radiotherapy (75%). Five patients (36%) presented profuse intraoperative bleeding, and at most recent follow-up 1 patient had died (mortality 7%). DISCUSSION: HPC accounts for <1% of primary CNS tumors and about 2.2% of all meningeal tumors. Clinical presentation varies according to tumor size and location. The main differential diagnosis remains meningioma. Radiologically, irregular margins and heterogeneous enhancement have been associated with aggressive behavior. Surgical resection is the treatment of choice validated by radiotherapy with doses over 50 Gy. Local recurrence incidence ranges from 26% to 80% depending on the extent of primary resection and administration of radiotherapy. Extra-neural metastasis rates range from 14% to 30% and are found predominantly in the bone, lungs, and liver, making strict follow-up mandatory.

CONCLUSION: Even a single clone with more advanced genetic progression cytogenetic pattern observed in a set of cells derived from the same tumor. Meningiomas show considerable intratumoral cytogenetic heterogeneity, particularly in their malignant form. We observed different cytogenetic heterogeneity in meningiomas, particularly in lack of other therapeutic options.

P.139. TREATMENT OF RECURRENT MENINGIOMAS WITH IMATINIB MESYLATE: A SINGLE-INSTITUTION EXPERIENCE

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BACKGROUND: Some 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, and 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 -beta and c-kit-targets were initiated with a daily oral dose of 400 mg imatinib mesylate as first-, second-, or third-line systemic therapy. MRI was performed every 3 months or at clinical suspicion of progression. The median time from diagnosis to start of imatinib treatment was 36 months. Immunohistochemical staining was performed on formalin-fixed and paraffin-embedded tumor tissue with antibodies against PDGFR-alpha, -beta, c-kit, arg, and abl. RESULTS: Imatinib mesylate at a dose of 400 mg/day was well tolerated. Of 9 patients treated with imatinib, 7 had stable disease and 2 progressed at the first scan after 3 months. We did not observe any complete or partial responses, though prolonged disease stabilization with a progression-free survival rate of 66.6% at 6 months could be observed. Overall median progression-free survival in the imatinib-treated cohort was 16 months (range 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.

P13 SPINAL CORD TUMORS

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

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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 5 “en bloc,” the others piecemeal), partial in 4. Histology showed myxopapillary type in 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 had been treated with radiotherapy. 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 an 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.

P137. INTRACRANIAL MENINGIOMA WITH EXTRANEURAL METASTASES: A SINGLE-INSTITUTION EXPERIENCE

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BACKGROUND: 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. Treatment options were determined with the presence of extracranial dissemination (LD) after surgery. METHODS: 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 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 period 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 subarchnoid 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 RECURRENCE 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 tree 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 meningioma 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.141. SPINAL CORD COMPRESSION FROM NEUROFIBROMAS IN NEUROFIBROMATOSIS TYPE 1 PATIENTS
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INTRODUCTION: Neurofibromas are characteristic tumors of Neurofibromatosis type 1 (NF1). They arise as discrete or more diffuse plexiform tumors, growing along cutaneous and subcutaneous nerves and spinal roots. Spinal neurofibromas are present in at least 50% of NF1 patients, and in most cases are asymptomatic. They are very different from sporadic Neurofibromatosis type 2–associated schwannomas in their cell composition, location, and behavior. There are scarce case reports and two small series with limited information, about clinical presentation and management of NF1 patients with spinal cord compression from spinal neurofibromas. The aim of the study was to review our experience in the management of these tumors. MATERIALS AND METHODS: A retrospective review of clinical data has been performed in our series of 205 NF1 patients, followed up, and treated in a 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 performance result data have been analyzed. 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 ranged from 29 to 51 years. Clinical presentation in 1 patient was quadriparesis in 3, paraparesis in 1, and monoparesis in 2 cases. The anatomical level was cervical in 4 and thoraco-lumbar in 2. Tumor was growing from either anterior or posterior roots. Large intraspinal tumors were radially resected in every case, sparing rootlets with small tumor nodules, through laminectomies or osteoplastic 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 quadriplegia, still presents a severe deficit, but 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 NF1. The risk of becoming symptomatic does not decrease with age. The cervical area is where more neurofibromas appeared, but caudal spinal cord was also affected. Resection of spinal root neurofibromas producing symptomatic spinal cord compression is followed by excellent functional results, except in patients with long-lasting severe neurological deficit. Although asymptomatic spinal neurofibromas should not be treated, surgery should be considered and planned as soon as symptoms appear for the best functional results.

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 I, II, or III, and the prognosis is excellent. Nonetheless, tumor recurrence rate after subtotal removal is 10%. CASE REPORTS: We present 3 cases of paraganglioma of the cauda equina, preoperatively diagnosed as an intradural mass on MRI. In 1997, a 41-year-old man presented with low back and radicular pain. Neurological examination revealed only sensory loss in the right leg, and MRI showed an intradural mass at L2–L3. In 1999, a 37-year-old man presented with low back pain and bilateral sciatica without neurological deficits. MRI showed an intradural mass at L3–L4. In 2005, a 51-year-old man presented with low back pain with bilateral irradiation to the gluteal region. No neurological deficits were present and MRI showed an intradural mass at L4. In all cases, a total resection of the tumor was performed after which all patients fully recovered. There is no recurrence in the last 11, and 5 years, respectively. CONCLUSION: Paraganglioma of the cauda equina is a rare tumor and we diagnosed 3 of such tumors on a total of 104 intradural extramedullary tumors (1994– 2005). All 3 cases presented with low back pain, as most often reported in the literature. No recurrence was seen in these 3 patients after total resection. In retrospect, MRI was not completely typical for Schwannoma or ependymoma, but the final diagnosis can only be made histologically.

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 paresis of the lower limbs. Cerebral 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 × 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 with a genetic multisystemic condition. 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 treat 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
P.145. BURKITT-LIKE LYMPHOMA REVEALED BY SPINAL CORD INVOLVEMENT
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Intramedullary spinal lymphoma accounts for only 3.3% of CNS lymphoma. It was mainly reported with immunodeficiency.1 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. Initial neurological examination showed only paraparesis. Immediate evolution was characterized by occurrence of an acute urinary retention and weakness of both hands. MRI of the spine showed multifocal intramedullary lesions, from C1 to C6, and upper thoracic spinal cord, diffusely enhanced by gadolinium injection. The same lesions were found in the brainstem and cerebellar lobes. Standard biological parameters, LDH, ß2-microglobulin, tumor markers were normal. Serological studies were negative. Blood protein immunoelectrophoresis found monoclonal lambda and kappa IgM. An extensive investigation, including chest and abdomen CT scan, bone marrow examination, ophthalmologic examination was negative. The level of CSF was increased (4.8 g/L), with a moderate lymphocytosis (19/mm3) without any abnormal cells. Surgical exploration showed involvement of spinal cord, intradural and arachnoidal tissue sparing epidural spaces. The diagnostic histological was high-grade B-cell lymphoma. The tumor had 2 populations, 1 of medium sized lymphoid cells with high nucleo-cytoplasmic ratio and 3 with irregular nuclei, with phagocytic macrophages giving a typical starry sky appearance (Figure 1b). Immunohistologically, the tumor cells expressed B cell antigen CD 20 and CD 45. The Ki 67 proliferative rate was near 100%. Bcl 2 was positive and Bcl 2 negative. No Epstein–Barr virus antigen was detected. These features led to the diagnosis of Burkitt-like lymphoma. The patient was treated by general polychemotherapy and intrathecal methotrexate. Treatment led to a decrease of the lesions size on further MR. The patient died from aplasia and respiratory distress syndrome after the third treatment.

DISCUSSION: BL accounts only for 1%–2% of lymphoma in adult, and is described as a variant of classic BL. It was mainly described in immunodeficient patients. BLL are high-grade, and are characterized by a poor initial 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 leptomeningeval dissemination and started an intracerebrospinal chemotherapy (IT) with methotrexate 30 Gy/10 # in May 2009. He obtained a complete response at CNS level and is alive and free of disease at 11 months after RT was done.

CONCLUSIONS: Among the rather uncommon localizations of MM in the CNS, myelomatous meningitis may also occur. Different modalities of treatment are used, including intrathecal chemotherapy, cranial irradiation, and systemic chemotherapy. Patients with CNS myeloma even with aggressive treatment have extremely poor prognosis with <3 month disease-free survival. However, the patient is still alive at 11 months after the involvement of CNS by MM has been diagnosed.

P.145*. CENTRAL NERVOUS SYSTEM (CNS) COMPLICATIONS OF MULTIPLE MYELOMA (MM): 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 difference in pathological mechanisms, clinical presentation, and therapeutic management. CNS involvement is the most frequent neurological complication in the small published series and account for about 70 cases reported in English literature.

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 leptomeningeval 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 received ASCT from a HLA-matched donor, achieving a 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 leptomeningeval dissemination and started an intracerebrospinal chemotherapy (IT) with methotrexate 30 Gy/10 # in May 2009. He obtained a complete response at CNS level and is alive and free of disease at 11 months after RT was done.

CONCLUSIONS: Among the rather uncommon localizations of MM in the CNS, myelomatous meningitis may also occur. Different modalities of treatment are used, including intrathecal chemotherapy, cranial irradiation, and systemic chemotherapy. Patients with CNS myeloma even with aggressive treatment have extremely poor prognosis with <3 month disease-free survival. However, the patient is still alive at 11 months after the involvement of CNS by MM has been diagnosed.

P.146* ROUTE OF INTRACREREOSPINAL FLUID LIPOSOMAL CYTARABINE ADMINISTRATION, SAFETY, AND EFFICACY OF THERAPY IN NEOPLASTIC MENINGITIS
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BACKGROUND: Recently, it has been reported by Ganz et al. that there was no difference between route of intracerebrospinal fluid chemotherapy administration, intraventricular vs intralumbar, with different drugs (eg, methotrexate or liposomal cytarabine) in terms of progression-free survival or overall survival. We present our experience in one single-center with liposomal cytarabine administered to patients with neoplastic meningits. METHODS: We reviewed 22 patients with cytologically documented neoplastic meningits because of solid tumor or haematological malignancies. All of them were treated with liposomal cytarabine. We examined the type of tumor (solid or haematological), overall survival (time from diagnosis till death or date of study), progression-free survival, and adverse events. RESULTS: Twenty-two patients were examined since December 2006 to March 2010. Seven of them received liposomal cytarabine by intraventricular administration; 15 by intralumbar infusion. Five had solid tumors and the rest haematological malignacies. Grade-1 adverse survival was 9.04 months (6.01 for the intralumbar group and 9.86 for the lumbar group). In the intraventricular group, only 1 patient had serious adverse event (ventriculitis). In the intralumbar group, 2 patients developed chemical cauda equine syndrome; 1 developed optic atrophy; and 1 developed both. CONCLUSIONS: Site of intra-CSF liposomal cytarabine is clinically relevant with fewer adverse events by intraventricular route.

P.146*. 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/daily 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 intravenous, every 4 weeks) and TMZ (150 mg/m2/day orally on days 1–5, every 4 weeks). Seven patients with melanoma were treated with combined chemotherapy of DDP (20/mg/m2/day intravenous on days 1–5, every 4 weeks) and TMZ (150 mg/m2/day orally on days 1–5, every 4 weeks). RESULTS: Observations of the
study were as follows: in the TMZ + WBI–treated patients with BM from NSCLC, 3 (14.3%) complete response (CR), 8 (38.1%) partial response (PR), 8 (38.1%) stabilization of disease (SD). The median overall survival (mOS) was 7.5 months. In the TMZ + WBI patients with BM from melanoma, 3 (17.6%) PR, 9 (52.9%) SD. The mOS was 6.6 months. Among patients with BC brain metasteses, 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 melano- noma, 1 (5.9%) CR, 4 (23.5%) PR, and 7 (41.2%) SD. The mOS was 6 months. In the TMZ + 1 patients with NSCLC brain metasteses, 7 (63.6%) SD. mOS was 8 months. In the TMZ – DDP patients with melanoma brain metasteses, 2 PR, 4 SD, 1 patient progressed. The mOS was 8 months. CONCLUSIONS: TMZ with WBI showed high efficacy in patients with BM from NSCLC, BC, and melanoma. TMZ as monotherapy showed efficacy and good tolerability in patients with BM from melanoma and SD in patients with BM from NSCLC. Combined chemotherapy of TMZ and I in heavily 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.

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 expect- ancy was more than 3 months if LM was controlled. The choice of treat- ment was based on clinical symptoms depending on the individual situation. Seven patients underwent intrathecal chemotherapy plus RT, EGFR-TKI plus RT, or VP-shunt plus RT (group A). Four patients under- went all of EGFR-TKI, RT, and VP-shunt (group B). Mean time to LM onset from diagnosis of lung adenocarcinoma was 24 (8–36) months. Mean survival time from LM onset was 4 months in group A and 9 months in group B (P = .029). Ten of 11 patients died; 9 of CNS metastases and 1 from pneumonia. No patients suffered from peritoneal carci- nomatosis after VP-shunt. CONCLUSION: Combination of triple modalities (EGFR-TKI, RT, and VP-shunt) is a safe treatment, and may improve outcome of patients with LM from lung adenocarcinoma.

NEUROTOXICITY AND NEUROPROTECTION

P.149*. IRRADIATED TUMOR VOLUME INFLUENCES LOCAL CONTROL AND PROGRESSION-FREE SURVIVAL IN PATIENTS WITH 1–3 BRAIN METASTASES TREATED BY RADIOSURGERY

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

BACKGROUND: Methotrexate (MTX) is an important chemotherapeu- tic 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 mimics cerebrovascular stroke. While this syndrome has been described in several case report series in children, it is much less frequently seen in adults. OBJECTIVES: To describe the clinical course of a patient with subacute toxicity after 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 leuke- mia 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 neurological syndromes. The acute or subacute neurotoxicity occurs within days to weeks after MTX therapy and is characterized by acute onset of focal neurological symptoms and mimics cerebrovascular stroke. While this syndrome has been described in several case report series in children, it is much less frequently seen in adults. OBJECTIVES: To describe the clinical course of a patient with subacute toxicity after 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 leuke- mia 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 enhancement and were only minimally hyperintense on T2 sequence. The patient’s neurological symptoms resolved completely over the next 24 hours without specific treatment. Repeat MRI 6 days later showed resol- ution of the diffusion abnormalites. DISCUSSION: Our case is unusual given the age of the patient. Most reports in the literature of subacute MTX toxicity describe children. 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 mis- diagnosed as presenting with an acute cerebrovascular ischemic or hemor- rhagic 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.
P.153. HLA-DQ2+ INDIVIDUALS ARE SUSCEPTIBLE TO HU-ANTIBODY ASSOCIATED PARANEOPLASTIC NEUROLOGICAL SYNDROMES

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BACKGROUND: Hu-antibody–associated paraneoplastic neurological syndromes (Hu-PNS) are diagnosed in patients with severe and subacute neurological syndromes through detection of high-titer Hu antibodies (Hu-Ab) in serum. Hu-Ab are directed against the neuronal Hu-D-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 analyze the role of T cells by determining whether human leukocyte antigen (HLA) association plays a role in Hu-PNS. PATIENTS AND METHODS: Frequencies of HLA-A, B, DR, and DQ alleles were determined in 53 Caucasian Hu-PNS patients with histologically proven SCLC and high-titer Hu-Ab. These were compared with the HLA types of 24 Caucasian SCLC patients without Hu-Ab or neurological symptoms and 2440 healthy, unrelated, Dutch Caucasian blood donors (HC). Odds ratios with 95% confidence intervals according to the Woolf test and two-sided Fisher exact test were used to compare the frequencies of the different HLA antigens in patients and controls. RESULTS: The frequency of HLA-DQ2 was significantly higher in Hu-PNS patients (33 of 53; 62%) than in HC (81 of 2360; 37%; P = .0015). Although there also was a trend towards a higher prevalence of HLA-DQ2 in Hu-PNS patients than in SCLC patients (7 of 24; 29%), this difference did not reach statistical significance, probably because of the small size of the SCLC patient group. Additionally, the HLA-DR3 frequency was significantly higher in Hu-PNS patients (25 of 53; 47%) than in HC (39 of 2360; 17%; P = .0022). DISCUSSION: This study indicates an association between Hu-PNS and presence of HLA-DQ2 and DR3 antigens. Both HLA-DQ2 and DR3 are part of the 8.1 ancestral haplotype (HLA-A1, Cw7, B8, DR3, and DQ2), which is a highly conserved HLA-complex associated with a wide range of autoimmune diseases. In Hu-PNS, the presence of HLA-DQ2 and DR3 suggests that these two MHC class II antigens are involved in the development of Hu-PNS diseases.

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

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INTRODUCTION: Neurological paraneoplastic syndromes (PNSs) are considered as rare, immune-mediated remote effects of systemic malignancy on nervous system. Long-term observations are not commonly performed and until now—in Polish population. The aim of this study was to evaluate the survival of PNS patients and its association with diagnosed malignancy as well as with onconeural antibodies (ONA). MATERIALS AND METHODS: The study included 177 PNS patients originating from Western Poland. In sera of all subjects, indirect fluorescence (EUROIMMUN, Germany) was performed as a screening and Western blotting (EUROIMMUN) as a confirmation test for the presence of ONA. The diagnosis of PNS was based on 'Graves' criteria. Five years after the confirmation of onconeural antibodies, the follow-up was performed in 57 patients after obtaining informed consent. Data for follow-up originated from medical records, personal (out-patients clinic) or telephone contact. RESULTS: A 5-year follow-up was performed in 57 patients, and malignancy was found in 11 cases. In 8 patients, primary tumor was diagnosed before or at the time of onset of PNS symptoms. The most common was lung cancer (32%), breast cancer (16%), ovarian cancer (16%), Hodgkin lymphoma (10.5%), and prostate cancer (10.5%). In the studied group, 16 patients had anti-Hu antibodies, 14 had anti-Ri, 14 had anti-Yo, 7 were undetermined, and 6 were seronegative. During the follow-up period, 8 patients died, 4 with diagnosed neoplasm, 6 had well-defined onconeural antibodies (1 with anti-Hu and 3 with anti-Ri). The number of patients with well-defined onconeural antibodies who survived 5-year period was higher (n = 38; P < .0001), than those without well-defined antibodies (n = 11). Also more patients (P = .0192) without diagnosed malignancy (n = 34) survived when compared with cancer patients (n = 15). CONCLUSION: The presence of well-defined onconeural antibodies in PNS patients is associated with better prognosis. Among well-defined onconeural antibodies, anti-Yo are predisposing to 3-year survival in Western Poland population.

P.155. NEUROLOGICAL PARANEOPLASTIC SYNDROMES AMONG WOMEN IN WESTERN POLAND: A STUDY FOCUSING ON OVARIAN TUMORS

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INTRODUCTION: The spectrum of primary malignancies in neurological paraneoplastic syndromes (PNSs) patients differs among males and females. In females, gynecologic and breast cancers are most frequently diagnosed. The aim of this study was to evaluate the prevalence of ovarian tumors among women patients with suspicion of NPS and neurological deficits or onconeural antibodies in ovarian tumor patients. MATERIALS AND METHODS: We included in the study 201 women from 395 patients with suspicion of NPS hospitalized in Department of Neurology in Poznan (Poland) in a time period 2002–2006. Based on Graus criteria, NPS were diagnosed in 113 females. In sera of all subjects, indirect fluorescence (EUROIMMUN, Germany) was performed as a screening and Western blotting (EUROIMMUN) as a confirmation test for the presence of onconeural antibodies. Eighty-five patients with ovarian tumors originated from subjects hospitalized between 2007 and 2009 in the Department of Gynecological Surgery in Poznan. RESULTS: Classical NPS were diagnosed more frequently (P < .00001) in patients with ovarian tumors (17%) than in subjects 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 higher than in cases without malignancy (3.16; CI 1.10–9.033, P = .0233). In females with nonovarian carcinomas, odds ratio of classical NPS was higher (6.65; 1.87–23.63, P = .0034). On the other hand, onconeural antibodies were found mainly (43%) in malignant ovarian tumors, and
P.156. INTRAVENOUS AND ORAL LEVETIRACETAM IN PATIENTS WITH MALIGNANT GLIOMAS: A PROSPECTIVE STUDY

O. Bahr,1, M. Hermisson2,3, S. Rona4, J. Rieger1, P. Körtvelyessy2, K. Franz5, P.157*. INTRAVENOUS AND ORAL LEVETIRACETAM IN PATIENTS WITH MALIGNANT GLIOMAS: A PROSPECTIVE STUDY

BACKGROUND: Levetiracetam (LEV) is a newer anticonvulsant with a novel mechanism of action. The aim of the study was to investigate the efficacy of LEV in patients with malignant gliomas. METHODS: In this prospective study, the efficacy and safety of LEV in patients with malignant gliomas were assessed. RESULTS: Of 20 patients enrolled, 17 patients completed the study. The median duration of treatment was 6 months. Treatment failure occurred in 3 patients. No serious adverse events related to the treatment with LEV occurred. CONCLUSIONS: Our study shows the feasibility and safety of oral and intravenous LEV in the perioperative treatment of brain 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.157*. INTRAVENOUS AND ORAL LEVETIRACETAM IN PATIENTS WITH A SUSPECTED PRIMARY BRAIN TUMOR AND SYMPTOMATIC EPILEPSY UNDERGOING NEUROSURGERY: THE HELLO STUDY

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BACKGROUND: 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 peripherally treated with oral and intravenous LEV up to 4 weeks before and until 4 weeks after a planned neurosurgical procedure. RESULTS: A total of 30 patients with brain tumor-related seizures and planned neurosurgery were included. Three patients did not undergo the planned surgery after enrollment, 2 patients were lost for follow-up. Therefore, 25 patients were fully evaluable. After initiation of therapy with LEV 100% of the patients were seizure-free in the pre-surgery phase (3 days up to 4 weeks before surgery), 88% in the 48-hour post-surgery phase and 84% in the early follow-up phase (48 hours to 4 weeks post surgery). Treatment failure after dose escalation to 3000 mg/day occurred in 3 patients. No serious adverse events related to the treatment with LEV occurred. CONCLUSIONS: Our data show the feasibility and safety of oral and intravenous LEV in the perioperative treatment of tumor-related seizures. Although this was a single-arm study, the efficacy of LEV appears to be promising. Considering the side effects and interactions of other anticonvulsants, LEV seems to be a favorable choice in the perioperative treatment of brain tumor-related seizures.

P.158. INTRAVENOUS AND ORAL LEVETIRACETAM IN PATIENTS WITH MALIGNANT GLIOMAS: A PROSPECTIVE STUDY

O. Bahr,1, M. Hermisson2,3, S. Rona4, J. Rieger1, P. Körtvelyessy2, K. Franz5, P.157*. INTRAVENOUS AND ORAL LEVETIRACETAM IN PATIENTS WITH MALIGNANT GLIOMAS: A PROSPECTIVE STUDY

BACKGROUND: Levetiracetam (LEV) is a newer anticonvulsant with a novel mechanism of action. The aim of the study was to investigate the efficacy of LEV in patients with malignant gliomas. METHODS: In this prospective study, the efficacy and safety of LEV in patients with malignant gliomas were assessed. RESULTS: Of 20 patients enrolled, 17 patients completed the study. The median duration of treatment was 6 months. Treatment failure occurred in 3 patients. No serious adverse events related to the treatment with LEV occurred. CONCLUSIONS: Our study shows the feasibility and safety of oral and intravenous LEV in the perioperative treatment of brain 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.

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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 significantly 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. Initial technical and clinical experience is described.

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

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 who underwent complete tumorectomy 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 7 of these patients (25%), intraoperative imaging depicted residual enhancing tissue leading to further tumor resection. In the iMRI group, a complete resection was achieved in 25 patients (89.3%) compared with 43 (60.3%) in the conventional group (P < .01). Mean age was 55.8 years, which did not differ between the iMRI guided and conventional microsurgery group (54.9 vs 56.2 years, P = .8). Until March 1, 2010, 23 patients have died. Mean follow-up was 50.5 weeks. Kaplan–Meier estimates rendered a mean overall survival of 91.1 weeks. There was no statistically significant difference between patients with primary vs secondary GBMs (P = .5). Young age (P < .01) and complete resection (P < .05) were associated with a better outcome. CONCLUSION: Even in dedicated centers, intended radiologically complete tumor resections cannot always be achieved in GBM surgery. In terms of extent of resection, the use of iMRI improves the surgical success rate compared with conventional microneurosurgical techniques. These results need further confirmation by a randomized trial.

NEW DEVELOPMENTS IN RADIOTHERAPY

P.162. DELIVERY OF WHOLE CEREBRO-SPINAL AXIS (CRANIOSPINAL) RADIOTHERAPY USING A SUPINE, INVERSE-PLANNED INTENSITY-MODULATED RADIOTHERAPY (IMRT) TECHNIQUE: CLINICAL EXPERIENCE IN 16 PATIENTS


BACKGROUND: A new technique using inverse-planned IMRT to treat the whole CNS in a supine position was introduced into routine clinical practice in 2008. Initial technical and clinical experience is described.

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

P.163. MEDULLOBLASTOMA IN ADULTS: LONG-TERM SURVIVAL AND TOXICITY IN 47 PATIENTS TREATED WITH SUPINE WHOLE CEREBRO-AXIS (CRANIOSPINAL) IRRADIATION

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BACKGROUND: Since 1972 craniospinal irradiation (CSI) at The Christie has been delivered supine with a parallel pair of cranial fields and matching posterior wedge pair fields to the spine. This is delivered conformally 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. Patients received 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 are alive and in remission. The 5-, 10-, and 20-year RFS are 61%, 52%, and 49%, and OS are 68%, 52%, and 43%, respectively. At last follow-up 27 live independently, 11 are employed, 9 are married, and 5 (3 males, 2 females) have had children post treatment. All relapsed patients had recurrent assessments and needed hormone replacement (3 growth hormone, 1 thyroxine, and 1 hydrocortisone). One patient developed epilepsy, 5 hearing impairment, and 2 second malignancies (breast, prostate). None developed meningioma, thyroid malignancies, or secondary BC at time of last contact. CONCLUSION: We report the longest follow-up data in adult medulloblastoma treated with a supine conformal radiotherapy technique. Our series is one of the largest and demonstrates survival comparable with published literature. Supine CSI is well tolerated by patients and reduces the long-term sequelae on the heart, thyroid, and gonads.

P.164. BORON NEUTRON CAPTURE THERAPY (BNCT): CLINICAL OPTIMIZATION OF UPTAKE PARAMETERS OF BORONOPHENYLALANINE (BPA) D. G. Ngoga1, G. Cruickshank1, A. Detta2, S. Green1, N. D. James2, C. Wojnecki2, J. Doran2, N. Graham1, Z. Ghani1, G. Halbert3, M. Elliot3, C. M. F. Dirven4, T. M. T. Shewen5, T. Vickerman1, K. Hyder6, C. G. Rosswell7, R. Sugar8, and A. Boddy91 University Hospitals Birmingham, Birmingham, UK; 2University of Birmingham, Birmingham, UK; 3CR-UK Formulation Unit, University of Strathclyde, Glasgow, UK; 4Regional Laboratory of the National Institute of Medical Research, Sandwell Healthcare Trust, Birmingham, UK; 5Surface Analysis Research Centre, The University of Aston, Birmingham, UK; 62University Hospitals Birmingham, Birmingham, UK; 7University Hospitals Birmingham, Birmingham, UK; 8University Hospitals Birmingham, Birmingham, UK; 9University Hospitals Birmingham, Birmingham, UK

INTRODUCTION: MGMT studies have demonstrated that a limited number of patients with glioblastoma benefit from Temozolomide. The remainder of the patients depend on radiotherapy at a maximum radiation dosage of 60 Gy, with no safe means of dose escalation. Boron neutron capture therapy (BNCT) is a binary treatment modality which represents a biologically targeted means of radiation dose escalation targeting both cyclic and noncyclical glioma cells 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 efficacy 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 macrodalsys), brain tissue around tumor and tumor tissue. Additional analysis was performed using Secondary Ion Mass Spectrometry (SIMS). RESULTS: Peak Boron (10B) levels in blood were in some patients until as late 6 hours after infusion, later than previously 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 eradication of irradiation at 1 hr after the end of BPA infusion.2 Our study shows delayed peak boron levels in brain and ECF suggesting that the optimal window for delivery of the radiation dose may be approximately 4 hours after infusion. Evasion 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 J. E. Gans , C. Stacey, N. Persh, D. D’Souza, and S. Short; University College Hospital, London, UK

INTRODUCTION: Patients treated for high-grade gliomas in the temporal region with external beam radiotherapy are at risk of significant cognitive 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 RapidArc® (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 reference 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 replanned using Varian RapidArc. Target volumes, organs at risk (OAR), and dose constraints defined for conventional planning were unchanged, but in addition hippocampi, inner ear, and temporal lobes were outlined using MRI fusion. No additional dose constraint was added for hippocampi. Comparisons of doses to the PTVs and organs at risk including hippocampi were then made. RESULTS: The conformality index was much improved with RapidArc (typically 1.5 with conventional and close to 1 with RapidArc). Formality 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 within the temporal lobe, the ipsilateral hippocampus was within the PTV, so dose could not be reduced. Dose to the contralateral hippocampus varied from patient to patient. In some the contralateral hippocampus, dose was larger because of the increased volume receiving low doses with RapidArc. CONCLUSION: RapidArc is effective at reducing dose to OAR near to the PTV, improving conformality 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 conformality does not lead to hippocampal damage, as expected, and may lead to the hippocampus being thought to be a dose-limiting structure.

MISCELLANEOUS

P.166. AWAKE SURGERY DURING RESECTION OF INSULAR GLIOMAS A. J. P. E. Vincent, R. Dammers, D. H. Kruijf, M. Klimek, and C. M. F. Dirven; Erasmus Medical Center, Rotterdam, Netherlands

PURPOSE OF THE STUDY: Insular gliomas are by many still considered inoperable, because of anatamical localization, vascular supply, and the potential devastating complications. We present our experience with the operative treatment of patients with insular gliomas in an “awake craniotomy” setting. PATIENTS AND METHODS: Nineteen consecutive patients with an insular tumor were operated awake during the period 2003–2009. Pre-operatively, an extensive neuropsychologic/linguistic workup was performed. All patients underwent MRI with neuronavigation and when possible fMRI. After cortical stimulation, the Sylvian fissure and periinsular sulci were defined for conventional planning were unchanged, but in addition hippocampi, inner ear, and temporal lobes were outlined using MRI fusion. No additional dose constraint was added for hippocampi. Comparisons of doses to the PTWs and organs at risk including hippocampi.2 Our study shows delayed peak boron levels in brain and ECF suggesting that the optimal window for delivery of the radiation dose may be approximately 4 hours after infusion. Evasion of tumor boron dose without additional dose to normal brain is possible and likely to further facilitate therapeutic response.

REFERENCES
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. In September 1999, 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 28-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 osteosarcomas 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 scl lym 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) protocol, he returned because of the 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 fMRI, DW MRI, spectroscopy, and MRV disclosed focal changes in the fronto-parietal regions with surrounding edema containing white matter. MRI findings were compatible with the signs of venous sinus thrombosis of the right transversal sinus and partial thrombosis of the 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 scl metastases, the residual retropertineal 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. Although the incidence of CVST in cancer is very low, it is of considerable clinical importance. This study adds to the current knowledge of CVST in cancer patients.

P.169. THE USE OF COMPLEMENTARY AND ALTERNATIVE MEDICINES (CAM) IN BRAIN TUMOR PATIENTS


INTRODUCTION: Complementary and alternative medicines (CAM) are known to be used by cancer patients, but there is an increasing interest specifically addressing their use in brain tumor patients and the incidence of CAM use in this group is unknown. We designed a questionnaire study to assess the use of CAM in brain tumor patients treated at University College Hospital, London between April and September 2009. 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 PETN. 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 degree of use and the use of CAM, with a particularly high use in the GBM group (70%). A range of different CAM were used, the most common being vitamins, reiki, reflexology, and acupuncture. 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. Seven patients spent considerable amounts of money on CAM, exceeding a thousand pounds. CONCLUSION: A very high incidence CAM use was reported in brain tumor patients, including males, which suggests a different pattern of use than has been documented in other cancer patients. A minority disclosed CAM use to the treating team. There have been reports of negative 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’s role place them in an ideal position to manage many of the radio-therapeutic aspects of care. However, paradoxically, there are few specialist radiographers in this discipline. At the Beatson West of Scotland Cancer Centre, we examined the patient treatment pathway and key elements were identified where the input of a dedicated Radiographer would feel liable to improve and optimize the delivery of care. Consequently, the role of a Neuro-Oncology Specialist Radiographer (Sp Rad) was established in November 2007. Elements were prioritized for introduction and protocols created incorporating ongoing assessment of competencies. The fundamental aspects of the Sp Rad role were identified early and quickly established: patient education regarding the process and delivery of radiotherapy; on-treatment assessment and management of toxicity; treatment verification with portal image review after training in anatomy recognition; and managing setup and immobilization issues for individual patients. More specialized tasks were gradually introduced, including identification and voluming of initially OAR’s then tumor volumes on the radiotherapy planning system (with subsequent checking by the neuro-oncology consultant); also a protocol was developed establishing CT-MR fusion for all Glioma patients receiving radical radiotherapy. The Sp Rad played a pivotal role in the development and implementation of the stereotaxy service and delivery of IMRT for selected glioma patients. The Sp Rad was instrumental in the drafting of clinical protocols (compliant with BMSIRI regulations) and related quality documentation for both of these technologies. The Sp Rad was also responsible for delivering a training package for radiographers and assessment of competence. The Sp Rad is currently the lead coordinator for a surgery-recovery service, liaising with the various therapeutic (MR) and therapeutic departments (simulation, planning, therapy delivery) as well as the patient to ensure rapid and efficient treatment delivery. The Sp Rad has been involved in other areas of service development, in particular creating a Pre-Treatment Assessment Clinic (PTAC), promoting governance and working with the CNS. The PTAC addresses the increasing complexity of
multi-modality therapy facing most glioma patients, including issues of patient and carer education, psychological adaptation, symptom control, the ongoing appropriateness of the therapeutic strategy, detailed planning and treatment, and obtaining informed consent. Key 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 32 females, with a mean age of 53.7 years (range 19.9–82.3). In 31 cases, there was a neuroimaging diagnosis exclusively, the other 16 had been operated on and had a pathologically confirmed diagnosis. In the surgical group, 3 patients had their lesions previously embolized, and 2 had received fractionated radiotherapy while in the nonsurgical group, 5 had received endovascular treatment, and 1 had fractionated radiotherapy.

At the time of treatment, 6% of the operated patients were asymptomatic, and 81% and 94% had low cranial nerve and VIII cranial nerve deficits, respectively. In the nonsurgical group, 3% were asymptomatic, with low cranial nerve involvement in 74%, and 71% and 23% with VIII and 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 5% (time of treatment, 6% of the operated patients were asymptomatic, and 81% and 94% had low cranial nerve and VIII cranial nerve deficits, respectively. In the nonsurgical group, 3% were asymptomatic, with low cranial nerve involvement in 74%, and 71% and 23% with VIII and V, VI, or VII cranial nerve deficits, respectively. The mean tumor volume was 14.2 cm³ (1.4–62.2 cm³), with a mean marginal dose of 13.6 Gy (12–15 Gy) and maximal doses between 20 and 55 Gy.

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recall, working memory, mental flexibility, and verbal fluency compared with normalized population, in the absence of anxiety or depression. Completion time test was ~1 hour. Recruitment of further patients and a control group matched by age, sex, and level of education is currently ongoing. CONCLUSIONS: The introduction of a battery of cognitive tests for cognitive and quality of life evaluation was feasible and well accepted by patients. This experience will serve as a basis for future development of cross-sectional and longitudinal studies of cognitive function and quality of life in patients with gliomas in our environment. There is a need for specialized neuropsychological assessment in neuro-oncology patients.

P.175. A LITERATURE REVIEW OF FIBRO-OSSEOUS PSEUDOTUMOR: THE ROLE OF SURGICAL EXCISION
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BACKGROUND: Fibro-osseous lesions are a rare clinical entity. We present the case of a 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 pseudo-tumor. 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 pathophysiology of these lesions was reviewed. RESULTS: Only 44 cases (28 intracranial, 16 spinal) have been reported to date. The majority occur in adults over 40, with a slight male predominance. Neurological symptoms result from local mass effect; however, seizures are also frequently observed. Imaging demonstrates central calcification with variable contrast enhancement. Histopathologically, a variably calcified chondromyxoid matrix with surrounding 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
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PURPOSE: To provide accurate, population-based incidence rate, prevalence rate, and mortality rate of primary brain tumor in the Chinese population. METHODS: We investigated 5 big communities in China. They were Baoshan district of Shanghai city, Long-nan district of Daqing city, Ma’anshan city, Shu-yan city, Pu-yang city. The incidence, prevalence, and mortality rates from October 1, 2003 to September 30, 2006 were measured. RESULTS: The incidence rate, prevalence rate, and mortality rate of primary brain tumors in the investigated areas were 10.5/100,000, 24.3/100,000, 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. POTENTIAL EFFECTS OF PARP INHIBITION ON CHEMO- AND RadiationTherapy Treatment in Serum-Free GLIOMA CULTURES
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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 preferably 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 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 radiation therapy (RT). METHODS: Freshly isolated HGG samples were cultured under SF conditions as neurospheres, SNP analysis of both low (p1–p4) and higher passages (p7–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 (a) TMZ (100 μM) and (b) ABT-888 (1 μM) for 6 days. 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 versus ABT-888 combination therapy. Of these samples, the clinical histological diagnosis was: GBM (n = 6) and anaplastic (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 potential synergistic effect on the TMZ resistance (≥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 6Gy 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.178. DEVELOPMENT OF A DRUG SCREENING ASSAY BASED ON PATIENT-DERIVED GLIOMA CELL CULTURES WITH GENOTYPIC RESEMBLANCE TO THE PARENTAL TUMOR
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INTRODUCTION: The culturing of cells that mimic the molecular and cellular aspects of gliomas is essential for the development of more reliable preclinical models for testing new drugs. We set up a protocol to efficiently grow low passage serum-free (SF) and serum-supplemented (SS) cell cultures from patient tumor material. We tested various coatings to allow growth of serum-free cultures in monolayers instead of neurospheres. The genotypic profiles of both SF and SS cell cultures were compared with the parental tumor, METHODS: Tumor tissue was enzymatically dissociated and split at equal concentration into either SF or SS conditions. SS cultured cells were split at 80%-90% confluence. SF cultured cells were grown as neurospheres (NS) or as monolayer cultures on various extracellular matrix (ECM) coatings. Expansion was scored as successful when cultures reached up to 5 passages, with expansion sufficient for pellet harvesting and low passage drug screening assays from p4 onward. DNA was isolated from snap frozen tumor sample or cell
pellets. For 3 individual patient series, we analyzed for copy number aberrations (CNAs) on Affymetrix SNP 6.0 arrays. RESULTS: In 12 months, a total of 39 glioma samples were collected; of which, 31 (32%) were propagated successfully. The success rate of SS cultures was solely dependent on the tumor size whereas the success rate in SF cultures was dependent on both sample size and initial amount of NS formation. SF tumor neurosphere cultures could be successfully transferred to monolayers in 96-well plates by seeding the cells on growth factor-reduced ECM coating, thereby attaining a model for drug screening. Successfully propagated tumors had similar genetic aberrations as the primary tumor. Genetic aberrations include high copy amplification of Chr.7p11 (EGER) and loss of Chr. 9p (CDKN2A) and Chr10, all of which are common genetic aberrations in gliomas. Some CNA became more apparent in SF cultures through selective clonal expansion. Importantly, SS cultures showed a gradual loss of CNAs in higher passages. CONCLUSIONS: We developed an efficient protocol for SS and SF culture derivation of surgically removed tissue. Using growth-factor reduced ECM coating, we are able to culture monolayers of GBM cells under SF conditions, which allows high throughput screening of patient-derived tumor cells with genetic profiles resembling the parental tumor up to high passages. However, the lower success rate of obtaining viable SF cultures remains a disadvantage. Moreover, we have determined the genetic aberrations of SS cultured material to be similar to tumor tissue in low passages (up to p4). This is, for practical and financial reasons, an attractive option next to SF cultures.

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

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