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NEURO-ONCOLOGY

Abstracts

ORAL PRESENTATIONS

CELL BIOLOGY AND SIGNALLING I

O.01. INHIBITION OF TGF-BETA SIGNALING IN GLIOMA CELLS BY THE INTEGRIN INHIBITOR CILENGITIDE

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Integrins have become a target for novel therapeutic strategies against malignant gliomas. Cilengitide, a synthetic Arg-Gly-Asp (RGD)-motif peptide, interferes with ligand binding to $\alpha v\beta 3$ and $\alpha v\beta 5$ integrins and is currently investigated in clinical trials. Integrins may also be involved in the activation of transforming growth factor (TGF)-β, a mediator of invasiveness and immune escape of glioma cells. Using flow cytometry, we demonstrate that the target integrins of cilengitide are expressed not only in glioblastoma blood vessels, but also by tumor cells. After exposure of glioma cells to cilengitide, we noticed reduced phosphorylation of Smad2 in most glioma cell lines, including stem-like glioma cells. Phophorylation of Smad2, but not cilengitide-induced detachment, is rescued by addition of recombinant TGF-β. Administration of cilengitide to glioma cells results in reduced TGF-β-mediated reporter gene activity. Furthermore, exposure to cilengitide leads to decreased TGF-β_1 and TGF-β_2 mRNA and protein expression. These effects are mimicked by blocking αv, $\beta 3$ or $\beta 5$ antibodies or by silencing of integrins αv, $\beta 3$, $\beta 5$ or $\beta 8$ using RNA interference. Treatment of mice bearing experimental LN-308 glioma xenografts with cilengitide results in reduced pSmad2 levels. Taken together, cilengitide may exert anti-invasive and immune stimulatory activity in human glioblastoma patients by its anti-TGF-β properties.

O.02. A NEURODEVELOPMENTAL PROGRAM AT THE CORE OF GLIOBLASTOMA STEM-LIKE CELL SELF-RENEWAL AND TUMORIGENICITY

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Glioblastoma (GBM) is the most common and malignant primary brain tumor. GBM prognosis remains dismal despite available treatments, because of tumor recurrence. According to the "Glioma Stem-like Cell" (GSC) hypothesis, GBM recurrence is sustained by a fraction of cells that share similarities with normal neural stem cells (NSCs). In potential agreement with this possibility, primary cell cultures with characteristics of GSCs can be established from GBM. These cells display typical hallmarks of NSCs, namely unlimited self-renewal and ability to differentiate into different neural lineages *in vitro*. Most importantly, GSCs are highly tumorigenic when transplanted intracranially *in vivo* and their *in vitro* self-renewal potential correlates positively with tumorigenicity and negatively with prognosis in glioma patients. We hypothesize that the tumor-forming potential of GSCs may result from the deregulation of molecular mechanisms normally involved in NSC self-renewal, proliferation and/or differentiation. In this regard, the fork-head transcription factor, FOXG1, promotes the self-renewal of both embryonic and adult NSCs. Here we show that FOXG1 mRNA and protein are upregulated in human gliomas and that elevated *FOXG1* expression is a bad prognostic factor in GBM patients. We show further that FOXG1 is expressed in a sub-population of GBM cells with NSC-like characteristics, as well as in cultured GSCs. More importantly, knockdown of FOXG1 significantly decreases GSC self-renewal, with a concomitant increase of the cell-cycle inhibitor, $p21^{Cip1}$. We also show that FOXG1 is co-expressed in GBM and GSCs with the transcriptional co-repressor TLE, a protein known to work together with FOXG1 during forebrain development. The effect of FOXG1 knockdown on GSC self-renewal is phenocopied by TLE knockdown, as well as by the forced overexpression of the previously characterized TLE:FOXG1 antagonist, GRG6, a protein with little or no expression in GBM. More importantly, mouse orthotopic implantations of human GSCs, which were either silenced for FOXG1 or overexpressing GRG6, gave rise to smaller tumors when compared to control condition; this tumor size reduction resulted in prolonged mice survival. Together, these results suggest that FOXG1 and TLE are important regulators of GBM tumorigenesis.

O.03. IDENTIFICATION OF NOVEL THERAPEUTIC TARGETS THROUGH AN INTEGRATED *IN VITRO* AND *IN VIVO* WHOLE GENOME SHRNA SCREEN IN GLIOMA STEM CELLS

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Anti-angiogenic therapy holds promise for the treatment of Glioblastoma (GBM), an aggressive brain tumor with dismal prognosis. However so far overall patient survival is barely improved and tumors quickly develop resistance mechanisms towards anti-angiogenic treatment. In preclinical GBM models we have recently shown that the anti-angiogenic agent bevacizumab induces a significant reduction in blood flow in treated tumors, which is accompanied by an increase in tumor invasiveness and hypoxia. Based on the hypothesis that GBM contain subpopulations of cells exhibiting stem cell properties (glioma stem cells) and are able to survive and thrive in a hypoxic environment, we undertook an integrated molecular analysis of the glioma stem cells to identify novel key regulators of survival under hypoxia. A functional shRNA lethality screen was performed on the glioma stem cell line NCH421k using the human GIPZ lentiviral shRNAmir library (Open Biosystems), containing more than 20,000 shRNA targeting about 9,000 well-annotated genes, from which we identified about 300 candidate genes that were essential for cell survival under long term hypoxia. Gene expression analysis of NCH421k cells, using whole-genome transcript analysis (Affymetrix GeneChip® Human Gene 1.0ST) revealed a strong up-regulation of genes involved in energy metabolism and autophagy under hypoxia. By integration of the lethality screen with gene expression data from cultured cells, as well as transciptomic data from patient GBM samples available from public databases, we defined a list of 56 candidate genes for *in vivo* validation. From the 56 genes, a pool of cell clones, each carrying a gene specific shRNA knockdown, was prepared for intracranial implantation in immunodeficient mice. The clones with genes essential for *in vivo* growth were expected to be lost during tumor development in vivo. Thirteen genes were found to be depleted in orthotopic tumors as determined by deep-sequencing. We have thus identified essential survival genes in glioma stem cells *in vivo* that represent novel molecular targets for drug development against highly resistant cells that cause tumor relapse.

O.04. GSK-3 AS A MULTIFUNCTIONAL TARGET FOR GLIOBLASTOMA TREATMENT; HITTING INVASION AND ANGIOGENESIS WITH A SINGLE DRUG

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Previous studies have shown that inhibition of GSK-3 (glycogen synthase kinase-3) can specifically block glioblastoma cell migration *in vitro*. Here we have tested this approach using *in vivo* orthotopic models of glioblastoma, and show a significant increase in survival in animals treated with GSK-3 inhibitors of the indirubin family. The data suggests that this is due to a combination of anti-angiogenic and anti-invasive effects. A panel of indirubin derivatives was examined in glioblastoma migration assays. A lead compound (bis-indirubin-acetoxime - BIA), was delivered by intraperitoneal injection in three separate orthotopic xenograft models (GBM9 glioblastoma stem cells, U87ΔEGFR, and X12 cells) and survival was monitored. Tumour sections were examined for the extent of invasion and blood vessel morphology. Three indirubin derivatives specifically and potently blocked glioblastoma cell migration *in vitro* in spheroid assays. These drugs blocked GSK-3 activity in treated cells as confirmed by Western blotting for β-catenin, and by a luciferase reporter assay. Treated animals survived twice as long as controls. Analysis of tumours revealed reduced invasion across the corpus callosum, and marked reduction in haemorrhage of treated tumours. Further examination showed a marked alteration in blood vessel morphology and density. Finally, we showed that indirubins block endothelial cell migration *in vitro*.

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Indirubins have anti-invasive effects on glioblastoma cells *in vitro* and *in vivo*. Treatment also has pronounced effects on tumour-associated endothelium. Thus we have identified an approach that combines anti-angiogenic and anti-invasive elements - a highly desirable combination of effects, and the subject of our ongoing investigations.

O.05. HYPOXIA-INDUCED DEATH OF GLIOBLASTOMA CELLS: TP53-INDUCED GLYCOLYSIS AND APOPTOSIS REGULATOR (TIGAR) HARMONIZES CELLULAR REDOX HOMEOSTASIS AND PROTECTS GLIOMA CELLS FROM HYPOXIA AND STARVATION BY UPREGULATION OF THE PENTOSE PHOSPHATE PATHWAY.

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Altered metabolism in tumor cells is increasingly recognized as a core component of the neoplastic phenotype. Since p53 has emerged as a master metabolic regulator, we hypothesized that the presence of wild-type p53 in glioblastoma cells could confer a selective advantage to these cells under the adverse conditions of the glioblastoma microenvironment. We recently reported that antagonism of p53 enhances the glycolytic phenotype and promotes hypoxia-induced cell death. At moderately hypoxic conditions, this effect was mediated by repression of synthesis of cytochrome c oxidase (SCO)2 dependent respiration. These findings demonstrated that glioma cells with p53 wild-type status can skew the Warburg effect and thereby reduce their vulnerability towards starvation at threshold oxygen concentrations in an SCO2-dependent manner. Here, we report on the effects of a second p53-dependent effector, Tp53-induced glycolysis and apoptosis regulator (TIGAR), on cell death induced by severe hypoxia. We demonstrate that TIGAR is overexpressed in glioblastomas, inhibits glycolysis and promotes pentose phosphate (PPP) way activation and glutathion regeneration. In contrast to modulation of SCO2, TIGAR regulated cell death also under severely hypoxic conditions. This effect correlated with enhanced ROS levels in TIGARsi-cells and was rescued by inhibiting the pentose phosphate transketolase isoenzyme TKTL-1. These findings suggest that glioma cells benefit from TIGAR expression by oxygen-dependent metabolic adaptation, enabling the harmonization of cellular homeostasis under the conditions of the tumor microenvironment. Targeting metabolic regulators such as TIGAR, especially by interfering with the PPP, may be a valuable strategy to enhance glioma cell sensitivity towards spontaneously occurring or therapy-induced hypoxia.

O.06. DNA DECOY OLIGONUCLEOTIDE THAT TARGETS THE MGMT ENHANCER CAN PROVIDE A NOVEL STRATEGY FOR CANCER TREATMENT

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INTRODUCTION: Alkylating agents show efficacy in the treatment of various tumors including gliomas. High cellular level of O(6)-methylguanine-DNA-methyltransferase (MGMT) counteracts the cytotoxic effect of alkylating drugs because it confers an efficient repair of DNA alkylation. Therefore, MGMT is an ideal target for pharmacological modulation. Two pseudosubstrates, O6-benzylguanine (O6-BG) and O6-(4-bromothenyl)-guanine that were intended to reduce MGMT activity failed to improve treatment outcome. The low efficacy outcome of these pseudosubstrates probably relates to the profound hematologic toxicity induced by the combined treatment with alkylating drugs and also to the rapid recovery of MGMT levels. Accordingly, the aim of the present study was to develop a treatment that will effectively and specifically reduce MGMT expression in tumors without cumulative toxicity in normal tissues. RESULTS: Our previous study revealed two NF-kappaB binding sites, MGMT-kB1 and MGMT-kB2 within the MGMT enhancer and identified the relationship between NF-kappaB and MGMT. Based on these findings, we assumed that interference with the binding of NF-kappaB to the MGMT enhancer will decrease MGMT expression level and thus may reverse MGMT-induced chemoresistance. For that purpose we designed locked nucleic acid modified decoy oligonucleotides (LMODNs), corresponding to the specific sequence of MGMT-kappaB1, the major NF-kappaB binding site associated with MGMT induction. We proved that LMODN interfered in a dose-dependent manner with the binding of NF-kappaB to the MGMT enhancer. The potential of the MGMT-kB1 decoy LMODN molecules to augment the efficacy of alkylating agents was studied *in-vitro* on three human cell lines. Treatment with MGMT-kB1-LMODN in concentrations of 2nM for T98G or 1 μM for MCF-7 and ACHN cell lines augmented temozolomide-induced cell killing by 2, 4.8 and 2.1 fold respectively. Furthermore, MGMT-kB1-LMODN monotherapy in concentrations of 4nM for T98G or 1 μM for MCF-7 and ACHN induced 70%, 79% and 68% cell killing respectively. CONCLUSIONS: Consistent with these observations, our results demonstrated that MGMT-kB1-LMODN given as monotherapy or in combination with temozolomide may provide a novel and effective approach for treating human cancers.

O.07. INTERACTION BETWEEN RADIATION, TEMOZOLOMIDE AND VALPROIC ACID ON MGMT PROMOTER METHYLATED AND UNMETHYLATED HUMAN GLIOMA CELLS

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OBJECTIVE: Current standard therapy for glioblastoma multiforme (GBM) patients consists of surgery, radiotherapy and the alkylating agent temozolomide (TMZ). Valproic acid (VPA), a commonly prescribed anti-epileptic drug in GBM patients, could potentially antagonize the effect of TMZ. VPA may cause DNA demethylation, and thereby induce expression of the O^6-methylguanine-DNA-methyltransferase (MGMT) protein, which is a dreaded cause of resistance to TMZ. We investigated the interaction between VPA, TMZ and irradiation on glioma cells *in vitro*. METHODS AND MATERIALS: Experiments were performed on a panel of five established and seven long term primary human glioma cell lines with known MGMT gene promoter status, MGMT protein expression and related sensitivity to TMZ. Cell survival was evaluated by the colony forming assay and protein expression by western blotting. VPA was administered 24 hr or 48 hr prior to γ-irradiation, with or without TMZ to a TMZ sensitive, MGMT negative (D384) and a TMZ resistant, MGMT positive (T98) cell line. The ratio of the radiation dose alone and the radiation dose for combination treatment with VPA, TMZ or both, i.e. the Dose Modifying Factor (DMF) was estimated at a cell survival level of 0.2. RESULTS: Clonogenic cell survival, tested following 24 hr exposure to TMZ in the dose range up to 500 μM, showed a clear discrimination between the TMZ sensitive and the TMZ resistant cell lines, which correlated with the expression of the MGMT protein. E.g., an isocytotoxic effect of ~10% cell sterilization by TMZ was found at ~5 μM for TMZ sensitive D384 and ~125 μM for the resistant T98 cell line. Both cell lines were tested in combination with irradiation, TMZ and VPA. TMZ demonstrated to be additive to irradiation on D384 cells, and to radiosensitize T98 cells. Also, 48 hr pre-incubation with 2.5 - 5 mM VPA enhanced the radiation response in both cell lines (D384: DMF = 1.4; T98: DMF= 1.5). Pre-exposure of glioma cells to VPA enhanced their sensitivity to TMZ (D384: DMF = 1.7; T98: DMF= 1.7). CONCLUSIONS:

- MGMT protein expression in glioma cells correlates with resistance to TMZ.
- TMZ has differential radiosensitizing potential. TMZ-induced clonogenic cell death was additive to irradiation, and might be synergistic. The radiosensitizing effect of TMZ is independent of the MGMT-promotor methylation status and of expression of the MGMT protein of the glioma cells.
- VPA does not antagonize but potentiates the cytotoxic effect of TMZ.
- Pre-treatment with VPA enhances the effect of the combination of irradiation and TMZ, in both the TMZ sensitive and TMZ resistant cell lines.

EPDEMIOLOGY & NEUROTOXICITY

O.08. THE ASSOCIATIONS BETWEEN GLIOMA SUSCEPTIBILITY LOCI AND PATHOLOGICAL PARAMETERS DEFINE SPECIFIC MOLECULAR ETIOLOGIES

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BACKGROUND: Genome-wide association studies have identified single nucleotide polymorphisms (SNPs) in seven loci at 5p15.33 (TERT), 7p11.2 (EGFR, two loci), 8q24.21 (CCDC26), 9p21.3 (CDKN2A/CDKN2B), 20q13.33 (RTEL1) and 11q23.3 (PHLDB1) influencing glioma risk. Since gliomas are heterogeneous tumors we investigated the relationship between SNP genotype and glioma subtype. MATERIALS AND METHODS: We studied the relationship between rs2736100 (5p15.33), rs11979158 and rs2252586 (7p11.2), rs4295627 (8q24.21), rs4977756 (9p21.3), rs6010620 (20q13.33) and rs498872 (11q23.3) genotype and IDH1 mutation, EGFR amplification, CDKN2A-p16-INK4a homozygous deletion, 9p and 10q loss, 1p-19q co-deletion in tumors from 1,374 patients. RESULTS:

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rs2736100 (5p15.33, TERT) and rs6010620 (20q13.33, RTEL1) risk alleles were associated with high grade, EGFR amplification, CDKN2A homozygous deletion, 9p deletion and 10q deletion; rs4295627 (8q24.21, CCDC26), rs498872 (11q23.3, PHLDB1) were associated with low grade gliomas, IDH1 mutation, 1p-19q codeletion. In contrast, rs11979158 and rs2252586 (7p11.2, EGFR) and rs4977756 (9p21.3, CDKN2A/B) risk alleles were independent of tumor grade and genetic profile. After multivariate analysis, rs2736100 (5p15.33, TERT), rs4295627 (8q24.21, CCDC26), and rs498872 (11q23.3, PHLDB1) risk loci remained associated with tumor alterations -loss of 10q, CDKN2A homozygous deletion and 1p19q codeletion- independently from grade. CONCLUSION: The frequency of EGFR and CDKN2A/B risk alleles were independent of tumor genetic profile, whereas TERT, RTEL1, CCDC26, PHLDB1 variants were associated with different genetic profiles which annotate distinct molecular pathways. Our findings provide novel insight into biological basis of glioma etiology.

O.09. INCIDENCE OF EMBRYONAL TUMOR WITH ABUNDANT NEUROPIL AND TRUE ROSETTES IN CHILDREN: A POPULATION-BASED STUDY BY THE AUSTRIAN BRAIN TUMOR REGISTRY

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BACKGROUND: Embryonal tumor with abundant neuropil and true rosettes (ETANTR) is a recently recognized embryonal CNS tumor, which predominantly affects young children and is associated with an aggressive disease course. Morphological keyfeatures include distinct neuropil islands and multilayered rosettes. Only recently, amplification at chromosomal locus 19q13.14 was described as genetic hallmark of ETANTR. As morphological keyfeatures might be inconsistent, systematic genetic testing contributes to diagnostic accuracy. Case reports and small case series point to a very rare disease. However, accurate population-based incidence data on ETANTR are not available so far. METHODS: A nation-wide survey on malignant high-grade CNS tumors, newly diagnosed in children (0-14 years) from 1996-2006 was conducted by ABTR. A central histopathology review was performed. In addition, FISH probes against chromosomal locus 19q13.14 were generated. RESULTS: A total of 311 newly diagnosed, malignant CNS tumors were included. Upon histopathology review three cases with characteristic morphological features of ETANTR were detected (age-standardized IR 0.21/1,000,000 person-years). 2/3 were diagnosed in female patients and supratentorial localizations. Median age at diagnosis was three years. Original histopathological diagnoses comprised medulloblastoma, CNS PNET, and ependymoblastoma. Another four tumors of the series exhibited morphological features suggestive but not diagnostic for ETANTR. Results of the genetic confirmation study are underway. CONCLUSION: This ABTR study uniquely combines population-based epidemiology with tissue-based analyses. First preliminary incidence estimates point to an exceedingly rare disease. Furthermore, the relation between morphology and genetics of ETANTR will be systematically addressed, thereby refining diagnostic criteria of this putative new entity.

O.10. GEOGRAPHIC DISTRIBUTION OF WHO DIFFUSE GRADE II AND III GLIOMAS IN METROPOLITAN FRANCE

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INTRODUCTION: Diffuse WHO grade II and III gliomas (DGII/IIIG) are rare tumors (incidence < 2/100 000 person-years). Specific epidemiological studies are very rare. The main objective of this work is to study the geographical distribution of newly diagnosed and histologically confirmed DGII/IIIG and finding clusters in metropolitan France. METERIALS&METHODS: The methodology is based on a multidisciplinary national network already established by the French Brain Tumor DataBase (FBTDB). Data from the FBTDB, supplemented by reporting of all cases from the listings of all pathology laboratories in France, allow recording all cases with newly diagnosed and histologically confirmed glioma. Personal addresses at the moment of the surgical procedure and surgical practices for all DGII/IIIG cases were also collected for the years 2006-2009. For each area, the number of DGIIG and the number of DGIIIG were analyzed and compared with the age distribution of the French population. The study was made with the participation of French societies and groups involved in the neuro-oncology field: Société Française de NeuroChirurgie (SFNC), Société Française de Neuropathologie (SFNP), Réseau d'Etude des Gliomes (REG), Association des Neuro-Oncologues d'Expression Française (ANOCEF). RESULTS: At present, we have already analyzed 1864 DGIIG (male/female: 56/44%, mean age at diagnosis: 44.6 years $\pm$15.9), 2135 DGIIIG (male/female: 57/43%, mean age at diagnosis: 53.9 years $\pm$16.4). At the moment, we are completing data for very few cases. Results for each type of DGII/IIIG (fibrillary astrocytoma, protoplasmic astrocytoma, gemistocytic astrocytoma, oligodendroglioma, oligoastrocytoma, anaplastic astrocytoma, anaplastic oligodendroglioma, and anaplastic oligoastrocytoma) will be presented. We will also present data for astrocytoma and glioma not otherwise specified. CONCLUSION: Until now, preliminary results show heterogeneity in the distribution of DGIIG and the distribution of DGIIIG among the French territory, with a higher number of cases in the northern, eastern and some central areas of France for both glioma groups. Even if small discrepancies exist between the two distributions (DGIIG/DGIIIG), they are globally comparable. This work is the first, to our knowledge, that studies the geographical distribution of diffuse grade II and III gliomas across one full country. If this heterogeneity in the geographic distribution of DGIIG and DGIIIG is confirmed, the authors will compare environmental, genetic and functional factors between areas with high incidence and areas with low incidence.

O.11. THE IMPACT OF RH/D BLOOD GROUP ANTIGEN ON INCIDENCE OF PRIMARY GLIOBLASTOMA MULTIFORME

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INTRODUCTION: The impact of Rh/D blood group antigen on incidence of various malignant diseases has been previously reported in the literature. AIM: We aimed to evaluate the correlation between Rh/D status and primary glioblastoma multiforme (GBM) development. MATERIAL AND METHODS: Rh/D phenotype was established in an unselected population of 109 patients with newly diagnosed GBM and the results were compared to 705 healthy donors. RESULTS: The presence of Rh/D negative phenotype was found to be significantly more frequent in the GBM cases ($p = 0.033$, OR = 1.8, 95%, CI = 1.1-3.0). CONCLUSION: The lack of Rh/D antigen seems to correlate with an increased risk of primary GBM development.

O.12. THE CHEMOTHERAPY-INDUCED PERIPHERAL NEUROPATHY OUTCOME MEASURES STANDARDIZATION (CI-PERINOMS)STUDY

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Chemotherapy-Induced Peripheral Neuropathy (CIPN) has not yet been investigated in a proper clinimetric manner, although it represents a potentially dose limiting complication of cancer treatment. As a result, inconsistencies are frequently found in the medical literature regarding clinically relevant aspects of CIPN. The aim of this study was to select appropriate outcome measures and to establish their validity and reproducibility in a cohort of cancer patients with CIPN secondary to various anticancer treatments. After literature review and a consensus meeting, the following scales were selected for the study the National Cancer Institute Common-Toxicity-Criteria (NCI-CTC), the Total Neuropathy Score (TNSc), the modified INCAT sensory sumscore (mISS), the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 and CIPN20 quality of life measures. At the 20 participating centers, 281 patients with stable CIPN were and the results underwent statistical analysis. For each scale the inter- and intra-rater agreement was evaluated by means of weighted K-Cohen coefficients and 95% confidence intervals, when

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analyzing qualitative ordinal scales and by means of Spearman's rank correlation coefficient and t-test when analyzing quantitative ordinal scales. The adopted weights for the estimate of K-Cohen coefficients were the Fleiss-Cohen weights. For validity purposes, the Kruskal-Wallis equality-of-populations rank test was performed relating the mISS and TNSc to the NCI-CTC grades. Inter-/intra-observer agreement was high (i.e. $r > 0.7$) for the TNSc, mISS, and NCI-CTC sensory/motor subscales. Once validity was investigated through comparison between the mISS and TNSc vs. the NCI-CTC scores acceptable validity scores were obtained (p values ranging from 0.04 to < 0.001). Test-retest values were high for the EORTC QLQ-C30 and for the CIPN20 subscale, although the autonomic module seemed to be less effective than the sensory and the motor ones to capture CIPN-specific features. These results, obtained in the largest ever performed methodological trial on CIPN, will provide a solid methodological background to future studies to be designed to investigate the scales' responsiveness issues.

This abstract is presented by G.C. on behalf of the CI-PeriNoms Study Group

O.13. PROSPECTIVE COHORT STUDY OF CAROTID INTIMA MEDIA THICKNESS AFTER IRRADIATION

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PURPOSE: Improving cancer treatment modalities result in more long term survivors, prone to late term treatment complications. Cerebral infarction is a devastating long term side effect of post-irradiation vasculopathy of the carotid arteries. The proposed pathophysiology is induction or acceleration of atherosclerosis by radiotherapy. The Intima Media Thickness (IMT) of the carotid artery is a valid method to measure atherosclerosis. The aim of the present prospective cohort study was to assess the change in carotid IMT and the incidence of cerebral infarction (CI) and TIA in the first two years after neck irradiation. METHODS: Prospective cohort study of 69 patients treated with neck irradiation because of head and neck cancer. The primary endpoint was the change in IMT from baseline to 2 years of follow-up. The secondary endpoint was the occurrence of cerebrovascular events. RESULTS: We found no significant increase in IMT between baseline and two years after neck irradiation. Change in IMT was associated with age at radiotherapy (RT) with a multiplicative effect per 10 years of 1.10 (95% CI 1.04-1.16, $p = 0.001$), but not with other baseline cerebrovascular risk factors. Within the first 2 years after RT, this study demonstrated an incidence of TIA and CI of both 15 per 1000 person years. CONCLUSIONS: We demonstrated an high incidence of CI and TIA but no increased carotid IMT in the first 2 years after irradiation of the neck. This suggests that other factors than postradiation angiopathy are involved. However, IMT may increase during a longer follow up period. Therefore, we will increase the follow-up period of the current cohort after RT.

O.14. BEVACIZUMAB FOR PROGRESSIVE RADIATION NECROSIS: PRELIMINARY RESULTS AND ONGOING CLINICAL TRIAL

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INTRODUCTION: Bevacizumab has been reported to be an effective treatment for symptomatic radiation necrosis and to decrease focal edema around areas of radiation necrosis. We report our preliminary results and ongoing clinical trial of bevacizumab treatment for radiation necrosis. METHODS: Thirteen patients with symptomatic radiation necrosis were treated with bevacizumab. Radiation necrosis was diagnosed according to the patients' clinical courses, magnetic resonance images, and fluoride-labeled boronophenylalanine-positron emission tomography (F-BPA-PET). Lesion/normal (L/N) ratios less than 2.0 and 2.5 on F-BPA-PET were defined as absolute and relative indications for bevacizumab treatment, respectively. The patients were treated with bevacizumab at a dose of 5 mg/kg every 2 weeks, 6 cycles in total. RESULTS: Two patients were excluded from analysis because of adverse events. Eleven patients underwent 3 to 6 cycles of bevacizumab treatment. The median rate of the reduction in peri-lesional edema was 65.5% (range: 2.0% to 81.0%). The Karnofsky performance status (KPS) improved in 6 patients after bevacizumab treatment, and in 5 patients the status did not change. The L/N ratio on F-BPA-PET ($P = 0.0084$) and the improvement of KPS after bevacizumab ($P = 0.0228$) were significantly associated with the reduction rate of peri-lesional edema after bevacizumab treatment. CONCLUSION: Bevacizumab is a very effective treatment for radiation necrosis, irrespective of the original tumor histology. F-BPA-PET could be useful for diagnosing radiation necrosis and for making the decision as to whether or not to treat symptomatic radiation necrosis with bevacizumab. The clinical trial "Intra-venous administration of bevacizumab for the treatment of radiation necrosis in the brain" has been approved as Investigational Medical Care System by Japanese Ministry of Health, Labour and Welfare. This trial has been ongoing since April, 2011.

QUALITY OF LIFE & SUPPORTIVE CARE

O.15. HEALTH-RELATED QUALITY OF LIFE IN SPOUSES OF GLIOMA PATIENTS COMPARED TO SPOUSES OF PATIENTS WITH NON-CNS TUMORS

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PURPOSE: The diagnosis, disease trajectory and treatment of a malignant tumor has a profound impact on the lives of both patients and their spouses. Spouses of patients with malignant tumors involving the central nervous system (CNS) often experience considerable stress and caregiver burden due to the changes in the patient's neurological and cognitive functioning. This, in turn, may have a negative effect on their health-related quality of life (HRQOL). In this study, we compared the HRQOL of the spouses of patients with high-grade glioma (HGG) and low-grade glioma (LGG), and the spouses of patients with cancer not involving the CNS (low-grade hematological malignancies (NHL/CLL) and non-small cell lung cancer (NSCLC). We hypothesized that partners of HGG patients would report significantly poorer HRQOL as compared to partners of LGG patients, and that partners of glioma patients would have poorer HRQOL than those of patients with non-CNS malignancies. METHODS: In this cross-sectional multi-center study, spouses of LGG, HGG, NHL/CLL and NSCLC patients completed the Short Form-36 (SF-36) Health Survey to assess HRQOL. LGG and NHL/CLL patients were diagnosed approximately 6 years prior to data collection, while spouses of HGG and NSCLC patients were included after initial diagnosis and prior to cancer treatment. RESULTS: 236 spouses of LGG patients, 107 spouses of NHL/CLL patients, 63 spouses of HGG patients and 35 spouses of NSCLC patients completed the SF-36. Multivariate analysis of variance with post-hoc Bonferroni tests for multiple testing revealed that SF-36 aggregate physical component scores (PCS) did not differ between groups. However, mental functioning of spouses of HGG patients as assessed by the SF-36 mental component scores (MCS) was significantly lower than that of spouses of LGG patients ($p < 0.001$) and spouses of NSCLC patients ($p = 0.022$). Furthermore, spouses of HGG patients reported less vitality ($p = 0.001$), poorer physical role functioning ($p = 0.012$), poorer emotional role functioning ($p < 0.001$) and poorer mental health ($p < 0.001$) than spouses of LGG patients. They also reported worse social functioning than both spouses of LGG ($p < 0.001$) and spouses of NSCLC patients ($p = 0.010$). CONCLUSION: Spouses of HGG patients, but not of LGG patients, are at increased risk of compromised HRQOL compared to spouses of patients with systemic tumors without CNS involvement and comparable life expectancy. Spouses of HGG patients need and deserve special attention and targeted interventions to enhance their HRQOL.

O.16. COGNITIVE FUNCTIONING AND HEALTH RELATED QUALITY OF LIFE IN LONG-TERM ANAPLASTIC GLIOMA SURVIVORS FROM EORTC STUDY 26951

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INTRODUCTION: Recent trials have shown that the addition of PCV chemotherapy to radiotherapy (RT) improves survival in anaplastic

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oligodendroglioma, especially in the presence of combined 1p/19q loss. With improved survival, quality of survival becomes pivotal. However, data regarding long term functioning in anaplastic glioma patients are virtually lacking. OBJECTIVE: To evaluate cognitive functioning and HRQOL in a cohort of Dutch and French long-term survivors from EORTC trial 26951 on adjuvant PCV chemotherapy in anaplastic oligodendroglioma or oligoastrocytoma. PATIENTS AND METHODS: 25 (17 AO, 8 AOA) of the 28 Dutch patients (89%; all Dutch participating centres) and 7 of 9 French patients (5 AO, 2 AOA; 78%; Paris centre) included in EORTC trial 26951 who were still alive agreed to participate. Cognitive functioning (assessed using neuropsychological tests for verbal and working memory, information processing speed (IPS), psychomotor function, attention and executive functioning) was compared with scores of matched healthy controls. Patients' HRQOL (assessed by means of the EORTC QLQ-C30 and BCM20 questionnaires) was compared with healthy controls, with the patients' own HRQOL 2.5 years following initial (RT) treatment and with the patient by proxy. Also general health and subjective cognitive functioning (MOS SF 36 and cognition scale) were assessed in patients and proxies, and fatigue (CIS) and mood (CES) in patients. Tumour histology, location and recurrence, treatment, the presence of epilepsy in the last year and use of anti-epileptics (AED) were recorded. RESULTS: Median survival of this group was 147 months. Compared to controls, 41% of patients did not show significant cognitive impairment (i.e. a z score of $\geq$2 SD below the mean of controls in at least one domain), 25% were mildly to moderately impaired (1-3 domains affected), and 34% were severely impaired ($\geq$4 domains affected). 31% of patients were employed, 78% were independent in ADL. HRQOL and general health of patients was worse compared to healthy controls, but was similar to 2.5 years after initial treatment. Treatment (in 35% of patients RT only, in 65% of patients RT/PCV), tumour histology and location did not significantly influence cognition or HRQOL. Current epilepsy was associated with worse IPS and verbal memory. Patients with recent recurrent disease (13%) had worse HRQOL, but their cognition did not differ from patients who were still progression-free. DISCUSSION: Cognitive performance in long-term anaplastic glioma survivors is variable. However, the majority of patients are able to function independently. Besides current epilepsy, we could not identify risk factors for disturbed cognition. HRQOL is relatively stable during the course of the disease, but is affected by recent recurrence. No effect of the addition of PCV to RT on cognition nor on quality of survival could be identified in this patient group.

O.17. ASSESSING THE IMPACT OF BRAIN CANCER IN CAREGIVERS' QUALITY OF LIFE (QOL)

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PURPOSE: The aim of the study was to analyze the impact of brain cancer in caregivers QoL and to compare this specific population to other oncology caregivers and to normative population in order to find differences and understand which aspects of QoL are more impacted. MATERIAL AND METHODS: The sample was composed of caregivers of patients with brain cancer from the Neuro-Oncology department of Timone University Hospital of Marseille, France. Control caregivers were selected from different oncology departments and were matched with caregivers of patients with brain cancer on age, sex and relationship with the patients (spouses, son/daughter, parent or sibling). We used the specific CareGiver Oncology Quality of Life questionnaire (CarGOQoL), a self-administered instrument comprising 29 items which is based on the exclusive point of view of caregivers to assess the impact of cancer and its treatment on caregivers' QoL. Caregivers also completed the Short Form 36 (SF36) for comparison to the French normative sample (a national representative sample of 3617 healthy French adults). RESULTS: The study sample included 50 caregivers of patients with brain cancer, aged 30-77 years, 28% of whom were men. Comparing specific CarGOQoL scores, significant differences were found for Burden and Leisure Time dimensions between cases and controls. Brain cancer caregivers had significantly lower scores for both dimensions, having an effect size of 0.4. Using SF36, no significant differences between cases and controls were observed. Compared to French age- and sex-matched normal controls, caregivers of patients with brain cancer had significantly lower mean scores for Social Functioning, Role limitation due to Physical health, Role limitations due to Emotional problems, Mental Health, Vitality and Bodily Pain. CONCLUSION: Caregivers of patients with brain cancer showed increased burden and lower scores for leisure time dimension. This could be explained by their unique care situation where patients become more limited physically and cognitively. Often changes in cognitive abilities, personality and behavior of the patient impact negatively in caregivers' QoL, changes that are less frequently presented in other cancers.

O.18. QUALITY OF LIFE CONCORDANCE BETWEEN PATIENTS WITH MALIGNANT GLIOMAS (MG) AND THEIR CAREGIVERS: FINAL DATA

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BACKGROUND: Quality of life (QOL) in patients with malignant gliomas (MG) is important. Patients often minimize many aspects of their deficits and overestimate their QOL making caregiver input very valuable. The purpose of this study was to investigate QOL concordance between patient and caregiver over multiple time points. METHODS: Patients with MG (grade 3 or grade 4 gliomas) within 6 months of diagnosis or relapse were eligible for this IRB approved study if they had an involved caregiver. The Functional Assessment of Cancer Therapy-Brain (FACT-Br) was given to patients and caregivers at baseline and then on the day MRIs were done for tumor assessment and continued until tumor progression or at least 3 pairs of data sets were collected. Patients filled out the FACT-Br and their caregiver filled out the same questionnaire based on how they perceived the patient should respond. MRI was done approximately every 2 months and questionnaires were given prior to disclosure of MRI results. RESULTS: 37 pairs of patient-caregivers were given FACT-Br. Included patients completed at least 4 sets of surveys total spanning at least a 6 month period; an additional 13 sets had less than 4 sets of data. Patients reported their overall QOL to be better than perceived by their caregivers by an average of 5 points on the 200 point scale ($p = .03$). Significant differences were found within subscales of physical ($p = .003$), functional ($p = .004$), and social ($p = 0.01$) well-being over at least a 6 month time window. CONCLUSIONS: A consistent discrepancy between patient and caregiver responses was seen with patients consistently reporting their QOL to be more favorable than perceived by their caregivers. This persisted throughout their disease course. This finding underscores the importance of including caregivers in clinical assessments to obtain a comprehensive view of patient QOL and functional status. Physician-caregiver communication is essential to ensure quality care and accurate assessment in patients with MG.

O.19. FINANCIAL BURDEN EXPERIENCED BY PATIENTS UNDERGIONG TREATMENT FOR MALIGNANT GLIOMA: FINAL DATA

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BACKGROUND: Patients undergoing treatment for malignant gliomas often face staggering costs outside of what is traditionally covered by insurance and beyond what is average compared to other solid tumors. These "out-of-pocket" costs are organized into these three categories: 1) direct medical costs (e.g. hospital stays, physician visits, laboratory testing); 2) direct non-medical costs (e.g. transportation, parking, food); and 3) indirect costs (e.g. lost wages). The purpose of this study is to gain prospective data regarding monthly expenditures associated with treatment of brain tumors. METHODS: Patients with grade III or IV malignant glioma within 6 months of diagnosis or relapse were eligible for this IRB approved study. Weekly logbooks were issued by patients to record out-of-pocket costs during treatment for six months or until progression. Both direct medical expenses and direct non-medical expenses were measured. Additionally, 9 quality of life (QOL) variables were obtained for patients with zero cost versus greater than zero cost. RESULTS: Thirty seven patients provided a mean of 12.5 weeks' worth of cost data each. Of the patients in this sample, 57% were male, 81% were married, 49% reported annual income greater than $75,000, and the average age was 53. Mean monthly out-of-pocket costs for this population were $2,153. These monthly expenditures are higher than those measured for select other cancer populations seen in the Robert H. Lurie Comprehensive Cancer Center, including lymphoma and breast cancer patients ($1,888 and $1,455 respectively)1. The greatest monthly costs were acquired in the form of medication co-payments ($499), transportation ($382) and hospital bills ($292). It was also shown that patients who did not have to pay for physical therapy and special equipment had a statistically significant greater emotional well-being and physical well-being. CONCLUSIONS: Out-of-pocket costs incurred by malignant glioma patients are particularly high and exceed costs in comparison to other solid tumors at our own institution. The treating physician must be aware of the particularly high financial burden on patients and their families undergoing treatment for malignant gliomas and consequent impact on the patient's and caregivers' well-being. As we have shown, working with patients and their families to minimize costs may even have a positive impact on the patient's QOL. These issues are important and should be further explored in a setting of changing domestic health care policy. 1 W. S. Oatis, N. Nonzee, T. Markossian, V. Shankaran, J. McKoy, A. Evens, L. Gordon, J. Winter, E. Calhoun, C. L. Bennett. Interpreting out-of-pocket

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expenditures for cancer patients: The importance of considering baseline household income information. J Clin Oncol 27:15s, 2009 (suppl; abstr 6541).

O.20. END OF LIFE AND GLIOBLASTOMA. SYMPTOMS AND TREATMENTS: DESCRIPTIVE ANALYSIS

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PURPOSE: Glioblastomas are among the most aggressive tumors. Few studies have analyzed during the end of life period (1) specific symptoms associated with central nervous system involvement (2) dedicated care. The aim of this study is thus (1) to evaluate the practices and results in a French neuro oncology centre (2) to compare them with literature data. METHOD: It is a single centre retrospective study. We analyzed files of adult patients treated for a glioblastoma diagnosed between 01/01/2008 and 31/12/2011 at our University Hospital of Nancy France and died between 1/07/2010 and 29/02/2012. The collection of data was done with three standardized forms (1) oncology form (2) places of residence and circuits during the last 90 days of life form (3) symptoms and treatments during the last 28 days of life form. RESULTS: Our population includes 53 patients. The circuit's analysis is underway. The main collected symptoms associate headache 17 %, epilepsy 40 %, level of consciousness 64 %, paresis 72%, dysphagia 55 %, confusion or agitation 36 %, incontinence 72 % and nausea or vomitting 25 %. Treatment strategies are highly varied. The detailed results will be presented inside a synthetic framework with a comparison with available literature data. CONCLUSION: This type of study is rare and will give us the opportunity to discuss changes in practice to consider. It could, we hope so, to contribute to the European group dedicated to the subject and being formed.

O.21. THE END OF LIFE PHASE OF HIGH-GRADE GLIOMA PATIENTS: DYING WITH DIGNITY?

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BACKGROUND: Patients with high-grade glioma (HGG) have a poor prognosis and can still not be cured. In the end of life (EOL) phase, HGG patients have a high symptom burden, frequently loose independence due to physical and cognitive dysfunction and often are unable to participate in decision-making. These factors might disturb the patients' personal dignity. The aim of our study was (1) to assess to what extent HGG patients died with dignity, (2) to determine how often predefined factors decreased personal dignity in HGG patients and (3) to identify disease and care factors related to dying with dignity in HGG patients. METHODS: We asked relatives of a cohort of 155 deceased HGG patients to fill in a questionnaire evaluating (1) whether the patient died with dignity, (2) issues threatening dignified dying, (3) quality of life, psychological and spiritual well-being close before death, (4) the EOL decision-making process and (5) quality of care. Factors possibly influencing dying with dignity were univariately (chi-square, fishers exact, t-test) and multivariately (logistic regression) analysed. RESULTS: Relatives of 81 patients completed the questionnaire. Seventy five percent indicated the patient died with dignity. 'Not being able to think clearly', 'being unable to communicate properly' and 'being unable to care for oneself' were most frequently mentioned as dignity-threatening factors in HGG patients. None of the predefined factors were significantly more often mentioned in reference to patients who did not die with dignity. We found that patients who died with dignity had less communication deficits, were more often at peace to die, experienced less transitions between health care settings in the last month of life, and more frequently died at their preferred place of death. Relatives of patients who died with dignity were more satisfied with the physician providing EOL care and perceived that this physician more often explained possible EOL treatment options. In the multivariate analysis, being satisfied with the physician providing EOL care, the ability to communicate, and the absence of transitions between health care settings in the last month were identified as most predictive factors for a dignified death. CONCLUSIONS: Satisfaction with the physician providing EOL care and the patients' ability to communicate at the EOL are important for a dignified death of HGG patients. Physicians caring for HGG patients in the EOL phase should explain possible treatment options at the EOL to patients and their involved relatives. As the majority of patients experiences communication deficits towards death, timely discussion of possible treatment options is advocated. Physicians should strive to letting the patients die at the preferred place of death and avoid transitions between health care settings in the last month of life.

IMMUNOTHERAPY AND BIOMARKERS

O.22. A FIRST IN MAN PHASE I TRIAL OF IMA950 (A NOVEL MULTI-PEPTIDE VACCINE) PLUS GM-CSF IN PATIENTS WITH NEWLY DIAGNOSED GLIOBLASTOMA - DESIGN AND PRELIMINARY RESULTS OF A CANCER RESEARCH UK STUDY

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BACKGROUND: Standard therapy for newly diagnosed glioblastoma (NDGBM) comprises maximal safe tumour resection, followed by concomitant chemoradiotherapy (CRT) and adjuvant temozolomide (TMZ). IMA950 is a novel multi peptide GBM specific vaccine that contains 11 HLA binding tumour-associated peptides (TUMAPs), which were identified on human leukocyte antigen (HLA) surface receptors in primary human GBM tissue, and one viral (HBV) marker peptide. The selected TUMAPs are designed to activate TUMAP-specific CD8+ cytotoxic and CD4+ helper T lymphocytes, which then recognise cognate TUMAPs presented by GBM tumour cells and effect a targeted immune response. The primary objectives of the current study are to assess the safety, tolerability and immunogenicity of IMA950 plus GM-CSF given alongside standard therapy in NDGBM which has been well resected. METHODS: Patients be eligible for standard treatment of GBM, and HLA-A*02 positive with no history of autoimmune disease. Vaccination comprises fixed doses of IMA950 plus GM-CSF injected intradermally at 11 time points over a 24 week period. Up to 45 patients with NDGBM will be entered. Three safety observation periods of 21 days are included after patients 1, 3 and 6 have completed treatment and prior to opening to general recruitment. Patients are recruited into one of two cohorts with similar schedules. In Cohort 1 vaccination begins 7 to 14 days prior to initial CRT; in Cohort 2 it begins a minimum of 7 days post CRT and 28 days prior to adjuvant TMZ. Safety is assessed according to NCI CTCAE Version 4.0. Immune response is determined by HLA-multimer analysis of vaccine-induced T-cell response in PBMC samples. Secondary objectives include observation of any anti-tumour effects, measurement of pretreatment regulatory T-cell levels and evaluation of the effect of steroid dose on observed T-cell responses. Retrospective analysis of diffusion and perfusion-weighted imaging is being performed to explore possible vaccination effects. Patients will also be followed up for overall survival. RESULTS: As of 29-Feb-12, 19 patients (9 in Cohort 1 and 10 in Cohort 2) have been recruited. Eighteen remain alive. Related adverse events have been restricted to minor injection site reactions and a single distant allergic rash. The first 6 patients have been fully analysed for immune response; all reacted positive for HBV peptide. Five subjects have responded to at least one TUMAP, 3 of these to multiple TUMAPs. CONCLUSION: These results vindicate the study design and will be fully updated; however they already give encouragement for further development of this vaccine.

O.23. IDH1 MUTATION: IMMUNOTHERAPY FOR MALIGNANT GLIOMA?

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Over 80% of grade II and grade III gliomas and secondary glioblastomas carry a mutation in the isocitrate dehydrogenase 1 (IDH1) gene, leading to an amino acid exchange at position 132, mainly R132H. The IDH1R132H

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status is used in histological diagnostics and defines glioma subtypes. IDH1 mutation is an early event during tumorigenesis and therefore exclusively and specifically expressed in all tumor cells, making it a glioma-specific antigen and an ideal potential target for immunotherapy of malignant glioma. With the aim of IDH1R132H-targeted vaccination therapy, we evaluated the immunogenic potential of IDH1R132H by assessing humoral and cellular endogenous immune responses in glioma patients and induced responses in vaccinated MHC-humanized mice. Using an overlapping IDH1R132H decameric peptide library covering the mutation region, CD8+ T cell responses in 30 IDH1R132H+ glioma patients to individual peptides were assessed in an IFNγ-ELISpot by stimulation of peripheral blood mononuclear cells (PBMC). There was no specific response detectable. Accordingly, peptide binding to MHCI HLA-A2 was negative in silico by SYFPEITII and NetMHC and in vitro by IFNγ-ELISpot competition and T2 binding assays. NetMHCII, however, predicted binding of distinct peptides of a 15aa IDH1R132H peptide library to MHCII DR1, which was confirmed by Reveal Class IITM binding and quick check stability assays. Cellular responses to a 20mer IDH1R132H peptide covering the library were analyzed in PBMCs from one glioma patient by purification of IFNγ-producing cells in an IFNγ catch assay. Flow cytometry revealed that the majority of cells were CD4+. In transgenic mice expressing human HLA-A2 and HLA-DR1, but not HLA-DR4 alone, peptide vaccination using complete Freund's adjuvant with the IDH1R132H 20mer and one 15mer peptide induced a mutation-specific IFNγ response to all DR1-binding peptides but not the decameric peptide library, illustrating a CD4+ T cell response. Ex vivo peptide restimulation of splenocytes followed by cytokine ELISA and intracellular flow cytometry revealed IL4 and IL17 responses, but no induction of CD25+ FoxP3 + , IL10-producing regulatory T cells. Regarding humoral responses, anti IDH1R132H IgG was detected in serum from boosted mice by ELISA. In line with this, IgG directed against two IDH1R132H peptides were detected in IDH1R132H+ glioma patients' serum. These data indicate mutation-specific cellular and humoral immune responses against IDH1R132H in IDH1R132H-vaccinated MHC-humanized mice and IDH1R132H+ glioma patients. Further analyses will reveal processing of the IDH1R132H protein and correlate patients' MHC haplotypes with anti-IDH1R132H IgG for the development of a diagnostic serum test for IDH1R132H. Therapeutic anti-tumor effects by IDH1R132H-specific vaccination will be determined in glioma-bearing MHC-humanized mice using clinically approved adjuvant.

O.24. CHARACTERIZATION OF BRAIN TUMOR-INFILTRATING CELLS AND COMPARISON WITH THE PERIPHERAL IMMUNE STATUS

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OBJECTIVE: The discordance between clinical and immunological data is a known problem for dendritic cell-based immunotherapeutic approaches for malignant glioma. A possible explanation for this lack in correlation might be that the peripheral immune status does not mirror the immune responses that occur in the tumor itself. Therefore, we wanted to establish a baseline phenotypical characterization of brain tumor-infiltrating cells (BTIC), which we could then compare to the immune status of the patient as measured in the peripheral blood. METHODS: BTIC were isolated out of fresh resection specimens of high-grade glioma patients that were not previously treated with immunotherapy. The isolated BTIC were used for phenotypical characterization by flow cytometric analysis. Comparison was made with fresh peripheral blood samples, which were obtained at time of surgery as well. Flow cytometric analysis was done for the following cell populations, relevant to the effector and suppressor arm of the immune system: CD4+ T cells; CD8+ cytotoxic T cells; CD4 + CD127dim(CD25+) regulatory T (Treg) cells; CD3-CD56+ natural killer cells; CD3 + CD56+ natural killer T cells; CD33 + CD11b + CD45 + CD15- myeloid-derived suppressor cells (MDSC). RESULTS: Phenotypical characterization of the BTIC, using flow cytometric analysis, showed that all cell types for which analysis was done, could be found to infiltrate gliomas. There was a significant higher percentage of suppressor cells (MDSC and Treg cells) in the tumor as compared to peripheral blood. Furthermore, there was no correlation between immune profiles in blood versus tumor. CONCLUSION: Our results show that the peripheral immune status does not mimic the intratumoral immune reaction. Treg cells and MDSC are attracted to the tumor, where they could enact an immune suppressive function, which would allow the tumor to evade the immune system This is in accordance with the model of 'cancer immunoediting', in which the tumor escapes the immune system in a final phase. Since there is a lack of correlation between immune profiles in blood versus tumor, the use of peripheral immune monitoring tools seems to be inadequate to measure the effect of immunotherapeutical approaches for glioma.

O.25. PROGNOSTIC OR PREDICTIVE VALUE OF MGMT PROMOTER METHYLATION IN MALIGNANT GLIOMAS DEPENDS ON IDH1 MUTATIONS

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PURPOSE: The clinical relevance of O6-methylguanylmethyltransferase (MGMT) promoter methylation and isocitrate dehydrogenase 1 (IDH1) mutation in malignant gliomas is controversial.The NOA-04 trial revealed MGMT promoter methylation in anaplastic gliomas as prognostic marker. Methylation of MGMT is associated with a striking increase in progression-free survival (PFS) independent of whether patients were treated with radiotherapy (RT) alone or alkylating chemotherapy alone. In contrast, in glioblastoma, MGMT promoter methylation is associated with increased PFS only in patients treated with RT plus temozolomide, but not RT alone. Here we analyzed the role of IDH1 mutations for this difference. Patients and Methods. Patients of the NOA-04 trial with known MGMT and IDH1 status (n = 183) were analyzed for interdependency of the prognostic versus predictive role of MGMT promoter methylation from IDH1 status and treatment, using PFS as an endpoint. An independent cohort of patients with anaplastic glioma or glioblastoma (n = 363) of the German Glioma Network (GGN) served as a confirmatory data set. RESULTS: MGMT promoter methylation was associated with prolonged PFS in both the chemotherapy $\pm$ RT and in the RT only group in both the NOA-04 and in the GGN cohorts in tumors with IDH1 mutation. In contrast, in tumors without IDH1 mutation, MGMT promoter methylation was associated with increased PFS in patients treated with chemotherapy, too, but not in those who received RT alone as the first-line treatment. CONCLUSIONS: The IDH1 status but not the WHO grade determines whether MGMT promoter methylation predicts benefit from either type of genotoxic therapy, RT or chemotherapy, or specifically benefit from chemotherapy in patients with malignant glioma. These data suggest that MGMT and IDH1 testing might help tailoring individualized therapy for malignant glioma patients.

O.26. CIRCULATING MICROVESICLES IN SERUM: COULD THEY SERVE AS A NEW DIAGNOSTIC TOOL FOR GBM PATIENTS?

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Glioblastoma (GBM) is the most common and malignant primary brain tumor in adults, and its prognosis remains dismal despite research and clinical advances. The identification of diagnostic and prognostic biomarkers for GBM in accessible specimens such as blood would be of considerable clinical importance. Recent findings have shown that GBM cells release microvesicles (exosomes) that contain a select subset of cellular proteins and RNA. These microvesicles are taken up by normal host cells such as microvascular endothelial cells and could also be released to the peripheral blood in other tumors. MicroRNAs (miRNA) are deregulated in cancer and have been proposed as biomarkers when isolated from blood and serum. This study was conducted to assess whether a miRNA signature in microvesicles isolated from the serum of GBM patients could serve as a diagnostic tool. First, the microvesicles isolated from the serum of GBM patients were morphologically and biochemically characterized by using Western blot, flow cytometry, electron microscopy and by size measurement. Two isolation methods were compared: gradient centrifugation and adsorption (Exoquick; SBI). The adsorption method yielded a higher amount of RNA and was found to be easier to use in a routine clinical setting. Next, the expression of 384 miRNAs using a PCR-based array (Applied Biosystems TaqMan® Low-Density Array) in RNA from microvesicles isolated from the serum of 25 newly diagnosed GBM patients and 25 healthy controls (paired by sex and age) was analyzed. Surprisingly, one snoRNA (RNU6) and two miRNAs (miR-320 and miR574-3p) were found to robustly differentiate GBM patients from healthy controls, being RNU6 alone the one that better differentiated patients from controls (AUC = 0.8824; $P < 0.0001$). These results were validated in the same cohort by qRT-PCR (AUC= 0.7628; $P = 0.002$). Furthermore, an independent cohort of 37 GBM samples and 27 healthy controls was used to validate these results (AUC = 0.787; $P = 0.0006$). Importantly, RNU6 expression was also found to be upregulated in 4 GBM specimens (tumor bulk and periphery) when

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compared with paired peritumoral tissue (from the same patient) or normal reference RNA. Our data suggest that small non-coding RNAs isolated from microvesicles of serum of GMB patients might be useful as a noninvasive diagnostic biomarker of GBM patients.

O.27. N-MYC DOWNSTREAM REGULATED GENE 1 CONTROLS TUMOURIGENICITY AND CHEMORESISTANCE IN THE HYPOXIC NICHE OF GLIOBLASTOMA

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BACKGROUND: The hypoxic microenvironment in glioblastoma (GB) serves as a 'germ center' for more aggressive and treatment-resistant tumour cell phenotypes. Understanding the molecular cues underlying hypoxic signalling might help to establish clinically relevant novel biomarkers and optimise current treatment approaches. METHODS AND RESULTS: Screening for novel hypoxia-linked key candidate molecules, we used a comparative 2D gel electrophoresis and mass spectrometry-based proteomics approach and identified N-myc downstream regulated gene 1 (NDRG1/CAP43/DRG1) as induced by chronic sublethal hypoxia in various human glioma cell lines. As opposed to the other members of the NDRG protein family, NDRG2-4, hypoxia-mediated induction was confined to NDRG1 and dependent on both hypoxia-inducible factor (HIF)-1alpha and -2alpha signalling. Moreover, expression of NDRG1 was also induced by irradiation in a p53-dependent, but HIF-independent manner. NDRG1 correlates with increased malignancy (WHO °II-IV) and shows a marked perinecrotic distribution pattern in GB. Lentiviral overexpression or RNAi-mediated gene silencing in glioma cell lines and sphere-forming primary cultures served as cellular tools to decipher anti-clonogenic, anti-angiogenic and anti-invasive effects for NDRG1 in vitro and in orthotopic mouse models. Notably, NDRG1 protected from temozolomide (TMZ)-induced G2/M-arrest and subsequent reduction of tumour cell proliferation. Analysing corresponding pairs of tissue specimens in GB patients revealed a strong increase in NDRG1 expression at relapse, suggesting a treatment-related selection for NDRG1-expressing cell populations and a potential role for NDRG1 in the recurrence of GB. In line with these findings, quantifying the NDRG1 status in tissue specimens of the UKT-05 GB trial, that evaluated dose-dense TMZ first-line therapy combined with standard radiotherapy, revealed a negative correlation between intratumoural NDRG1 expression and progression-free as well as overall survival. CONCLUSIONS: NDRG1 is a novel key regulator of tumourigenicity in the hypoxic niche of GB that mediates resistance to clinically relevant treatment modalities. Our findings shed light on the role of hypoxia in the adaption to chemotherapeutic treatment and introduce NDRG1 as a promising candidate for targeted therapy.

O.28. THE T GENOTYPE OF THE MGMT C > T (RS16906252) ENHANCER SNP IS ASSOCIATED WITH PROMOTER METHYLATION AND LONGER SURVIVAL IN PATIENTS WITH GLIOBLASTOMA

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Clinical studies in patients with newly diagnosed glioblastoma have shown that the methylation status of the MGMT gene is both predictive and prognostic of outcome. The C > T SNP (rs16906252), located within a cis-acting enhancer element at the first exon-intron boundary of MGMT that is required for efficient promoter activity, is a key determinant in the acquisition of MGMT methylation in several solid cancers. We now demonstrate a correlation between MGMT methylation and presence of the variant T allele in the context of glioblastoma. A significant survival advantage was observed for patients who had MGMT promoter methylation and also harbored the T allele in glioblastoma, compared to those with MGMT promoter methylation and wild-type at this SNP site. T allele carriers also had improved survival compared to those with the wild-type genotype, irrespective of methylation status. Promoter reporter experiments in the U87 and U251 glioblastoma cell lines showed the T allele conferred a 30% reduction in normalised MGMT promoter activity compared to the wild-type haplotype. This might account for the improved survival observed in the T allele carriers, with or without MGMT methylation.

O.29. ELUCIDATION OF DNA REPAIR SIGNATURES THAT CONFER RESISTANCE TO TEMOZOLOMIDE AND POOR SURVIVAL IN PATIENTS

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Glioblastoma multiforme (GBM) is the most common and lethal of all gliomas. The current standard of care includes surgery followed by concomitant radiation and chemotherapy with the DNA alkylating agent temozolomide (TMZ). O6-methylguanine-DNA methyltransferase (MGMT) repairs the most cytotoxic of lesions generated by TMZ, O6-methylguanine. Methylation of the MGMT promoter in GBM correlates with increased therapeutic sensitivity to alkylating agent therapy. However, several aspects of TMZ sensitivity are not explained by MGMT promoter methylation. Here, we investigated our hypothesis that the base excision repair enzyme alkylpurine-DNA-*N*-glycosylase (APNG), which repairs the cytotoxic lesions N3-methyladenine and N7-methylguanine, may contribute to TMZ resistance. Silencing of APNG in established and primary TMZ-resistant GBM cell lines endogenously expressing MGMT and APNG attenuated repair of TMZ-induced DNA damage and enhanced apoptosis. Reintroducing expression of APNG in TMZ-sensitive GBM lines conferred resistance to TMZ in vitro and in orthotopic xenograft mouse models. In addition, resistance was enhanced with coexpression of MGMT. Evaluation of APNG protein levels in several clinical datasets demonstrated that in patients, high nuclear APNG expression correlated with poorer overall survival compared with patients lacking APNG expression. Loss of APNG expression in a subset of patients was also associated with increased APNG promoter methylation. Collectively, our data demonstrate that APNG contributes to TMZ resistance in GBM and may be useful in the diagnosis and treatment of the disease. These observations lead us to investigate the global impact of DNA repair signatures in GBM in predicting TMZ resistance or sensitivity. We analyzed over 400 DNA repair genes in over 200 GBM samples. Using Non-negative matrix factor clustering (NMF) we identified two groups of GBM with altered DNA repair signatures in which age was not significantly different. Group A comprised of patients with poor overall survival (<12 mos) and was enriched for the mesenchymal subtype whereas Group B had better overall survival (>16mos) and was enriched for the proneural subtype. Poor prognosis Group A tumours contained a higher frequency of mutations in mismatch repair genes including MSH2 and aberrant expression in base excision repair proteins including APEX1 and APNG. These results were validated in 2 additional datasets. Collectively we demonstrate that altered DNA repair protein expression profiles can identify patients more likely to be resistant to treatments such as TMZ and provide evidence for targetting certain DNA repair pathways for more effective therapeutic strategies.

NON-GLIAL TUMORS AND IMAGING

O.30. RECURRENT HIGH-GRADE MENINGIOMA: PHASE II TRIAL WITH SOMATOSTATIN ANALOGUE THERAPY

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INTRODUCTION: Standard therapy for high-grade meningioma patients includes surgical and radiation therapy. Recurrence after the completion of both therapies is managed by re-resection, although several therapies, including hidroxyurea, alpha-interpheron and somatostatine analogue (STa) have been suggested as possible useful complementary treatments. However, STa has demonstrated contradictory results in terms of radiographic response between phase II trials. OBJECTIVES: A prospective phase II trial with long-acting STa in patients with recurrent high-grade meningioma was conducted. Primary study endpoint was radiographic partial response (PR). Secondary endpoint was progression free survival at 6 months (PFS6). METHODS: Inclusion criteria: Patients with radiological high-grade meningioma progression after prior surgery and radiotherapy were included. Recurrence was not accessible to re-resection. All had positive brain octreotide SPECT scanning tumours at recurrence. Treatment: STa was administered once every 28 days at a dose of 30mg for the first two cycles and 40mg for subsequent cycles. Follow-up and assessment: Magnetic resonance imaging (MRI) was performed every 3 months. Progression and PR was

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defined as an increment of ≥25% and as a decrement of ≥50% of two-dimensional maximum diameters, respectively. STa was maintained until progression. Statistics: A two-stage phase II trial was designed. The target accrual was 7 patients in stage 1 and three or more radiographic responses (PR) were needed to continue to stage 2. RESULTS: Seven patients (6 men; median age 63) with high-grade recurrent meningioma (5 grade II and 2 grade III of WHO classification) were included. Patients received a median of 3 STa cycles (range 3 to 8 cycles) without grade ≥2 toxicities. No partial radiographic responses were observed. Stable disease was the best response in 29% (n = 2). No patient had neurological improvement. All patients had progressive disease at 10 months of follow-up. Median time to progression (TTP) was 4.23 months (range 2.82 to 9.38) and the PFS6 was 43% (n = 3). CONCLUSION: None patient demonstrated a partial radiographic response with monthly long-acting STa schedule. Modest median TTP of 4-5 months joint to the unknown natural history of recurrent meningiomas, make uncertain the use of this therapy in recurrent high-grade meningioma.

O.31. OUTCOME OF LOW-DOSE ORAL ETOPOSIDE TREATMENT IN REFRACTORY AND RECURRENT CENTRAL NERVOUS SYSTEM GERM CELL TUMOURS

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PURPOSE: The outcome for patients with recurrent germ cell tumor is sometimes very poor, even with aggressive treatment with high-dose chemotherapy and/or re-irradiation. This is the retrsospective analysis of 8 patients treated with low-dose oral etoposide for the1st to 4th recurrence. PATIENTS AND METHODS: Eight patients(3 with germinoma and 5 with mixed malignant germ cell tumor) age 10 to 31 years were treated with VP-16 after neuroradiographic and clinical evidence of tumor progression. All had received prior irradiation and six of them received re-irradiation for recurrence. All had been pretreated with a variety of chemotherapeutic agents and schedules, and four of them had recurrent lesions after high-dose chemotherapy. VP-16 was administered orally as repeated 21-day course at 50 mg/m2/d with 7- or 14-day interval between courses. In one patient the dose was reduced to 25/m2/d for active infection. RESULTS: The major toxicity of oral VP-16 was hematologic, with one patient requiring platelet transfusion due to thrombocytopenia. Though all patient developed treatment-related mild neutropenia, there was no need for support with granulocyte colony stimulating factor(G-CSF). There was no treatment-related death. Of 8 patients assessed, two demonstrated complete response(CR), two partial response(PR) and three stable disease(SD) and one progressive disease(PD). Response in tumor marker(beta-HCG and/or AFP) was observed in seven. Progression free survival was >4months, >5months, 11months, 12months, 27months, >27months, >49months in each responders. CONCLUSIONS: This demonstrates the good activity of oral etoposide in the treatment of heavily pretreated patients with recurrent germ cell tumors refractory to any kinds of treatment including craniospinal irradiation and high-dose chemotherapy. This treatment can have a new role in the earlier course of the treatment.

O.32. COMBINED SYSTEMIC POLYCHEMOTHERAPY AND INTRATHECAL TREATMENT WITH LIPOSOMAL CYTARABINE IN PATIENTS WITH PRIMARY CNS LYMPHOMA ≥ 60 YEARS: RESULTS OF A PHASE II-TRIAL

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OBJECTIVES: To evaluate response rate, event-free survival (EFS), overall survival (OS), and toxicity in patients ≥ 60 years with primary central nervous system lymphoma (PCNSL) after combined systemic and intrathecal chemotherapy. PATIENTS AND METHODS: From 11/2005 to 02/2010, 89 patients with PCNSL (median age 68 years, range 60-76) were enrolled into a multicenter phase II-study evaluating combined systemic and intrathecal polychemotherapy. A high-dose methotrexate (MTX) (cycles 1,2,4,5) and cytarabine (ara-C) (cycles 3,6) based systemic therapy (including dexamethasone, vinca-alkaloids, ifosfamide and cyclophosphamide) was combined with liposomal cytarabine administered intrathecally via lumbar puncture once during each treatment cycle. EFS and OS were calculated from time of histopathological diagnosis to time of progression, toxic death or interruption of therapy for any cause and death, respectively. RESULTS: From 89 patients enrolled, 68 were evaluable for response, nine (10%) died due to treatment-related complications and in 12 (14%) therapy had to be discontinued due to treatment related complications. In one patient response could not be evaluated by imaging because of an asymptomatic cerebral hemorrhage. According to the IPCG response criteria (J Clin Oncol. 2005 Aug 1;23(22):5034-43) 44/89 (49%) achieved complete response (CR) or complete response unconfirmed (CRu), 7/89 (8%) partial response (PR), and 16/89 (18%) progressed under therapy. Follow-up is one to 64 months (median 12 months). Kaplan Meier estimates for EFS was 8 months (95% CI 3.9-12.1), median OS was 22 months (95% CI 9.6-34.4). The 5-year survival fraction was 33 %. Toxicity (WHO III/IV) was mainly hematologic (100 of 428 cycles) and infectious complications (WHO III/IV) occurred in 48 / 428 cycles. CONCLUSIONS: EFS and OS with this combined systemic and intrathecal chemotherapy are similar to what has been achieved with other protocols in elderly patients with PCNSL. However, one third survived longer than 5 years with this regimen and the overall disappointing results may be in part attributable to a considerable rate of treatment related complications.

O.33. PRESENTATION, DIAGNOSTICS AND TREATMENT OF PRIMARY LEPTOMENINGEAL LYMPHOMA: AN INTERNATIONAL PRIMARY CNS LYMPHOMA COLLABORATIVE GROUP SERIES

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Primary leptomeningeal lymphoma (PLML), without parenchymal central nervous system (CNS) or systemic involvement is very rare; only small case series, the largest of which included 9 patients, have been reported. We identified 48 PLML patients from 12 institutions between 4/81 and 11/11. Inclusion required pathologic confirmation by CSF analysis or meningeal biopsy, no prior history of systemic or CNS lymphoma, and no concurrent evidence of intraparenchymal CNS. Median age at diagnosis was 51 years (range 6-84) and median KPS 70 (40-90) [ECOG 2 {1-4}]. Median time to diagnosis was 2 months (0-30 months). The most common presenting symptoms included cranial neuropathies (54%), radiculopathies (48%), and headaches (44%). MRIs were abnormal in 87% with leptomeningeal enhancement identified in 100% of cases. Overall, CSF was diagnostic in 79%, with median number of lumbar punctures required for diagnosis of 2 (range 1-5). Cytology was abnormal in 53% and molecular markers (IgH or TCR gene rearrangement) diagnostic in 67% (14/21) of cases, whereas flow cytometry was diagnostic in 90% (27/30). Notably, three of the samples with positive flow cytometry had an otherwise normal CSF profile. Meningeal biopsy was required for diagnosis in 21% of cases. 76% of cases had B cell lymphoma, 22% T cell lymphoma, and 2% anaplastic lymphoma. The most common treatment was systemic chemotherapy, which was used in 39%, with 86% of regimens including high-dose methotrexate. Upfront radiation was used in 37%. The combination of systemic and intra-CSF chemotherapy was used in 20% and 15% were treated with all three modalities. The best clinical outcome was a complete response, noted in 43% of patients; median response duration was 4 months (range 0-121 months). There was no correlation between the initial treatment modality and response duration or overall survival. 44% of patients relapsed: 19% with intraparenchymal CNS disease and 9% systemically. Median overall survival was 18 months (0-121 months) with 4 patients surviving longer than 5 years. In conclusion, PLML is a rare manifestation of primary CNS lymphoma that presents like other forms of neoplastic meningitis and in which CSF cytometry is often diagnostic. Though treatment varies widely and the median overall survival is limited, long-term survival is possible.

O.34. MRI-BASED VESSEL FUNCTION MAPS FOR HIGH RESOLUTION DIFFERENTIATION BETWEEN TUMOR AND NON-TUMORAL TISSUES IN BRAIN TUMOR PATIENTS

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BACKGROUND: Changes in enhancement seen in post treatment brain MRIs in primary and secondary brain malignancies often mimic tumor

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progression (pseudoprogression, radiation necrosis). Conventional MRI cannot differentiate tumor progression from treatment related effects resulting in suboptimal patient management. METHODS: The application of delayed contrast extravasation MRI for depicting unique vessels characteristics with high resolution and high sensitivity to subtle BBB disruption is demonstrated in 17 GBM and 17 brain metastases patients undergoing standard chemoradiation and radiosurgery respectively. RESULTS: 2 primary vessel function populations were determined: a slow population where contrast clearance from the tissue was slower than accumulation, and a fast population where clearance was faster than accumulation. 16 stereotactic samples acquired from GBM patients showed complete correlation with the maps, confirming the discrimination between fast population regions, reflecting morphological active tumor (hyper cellularity, small cells, mitosis, high Ki67, pseudo-palacading necrosis, vascular proliferation) and slow regions reflecting necrosis/treatment-induced changes (radiation changes including large, widely spaced atypical astrocytes, blood vessels hyalinization, fibrinoid material in vessels, proliferating small vessels, tumor necrosis). Typical fast population vessel morphology consisted of proliferating endothelial cells, dilated lumen, peri vascular fibrosis and glumeroloid vessels, while slow regions consisted of necrotic vessels, in agreement with the observed MRI vessel function. Significant correlation ($r^2 = 0.54$, $p < 0.0006$) was found between the blue population growth rates and time to progression. Increase in the fast population volume was followed by progression while increase in the slow population was not (pseudoprogression). Brain metastases histology showed similar results: 6 brain metastases with a fast population component were confirmed histologically to contain morphologically active tumor. One metastasis consisting of the slow population only was confirmed as radiation necrosis and another significantly decreased in volume in the following MRIs, consistent with radiation necrosis. CONCLUSIONS: These results demonstrate the feasibility of applying our delayed contrast extravasation high resolution vessel function maps for improving patient management by clearly depicting tumor and non-tumoral tissues in patients with primary and secondary brain malignancies undergoing standard chemoradiation or radiosurgery.

O.35. SUSCEPTIBILITY WEIGHTED IMAGING PREDICTS PROGRESSIVE DISEASE IN PATIENTS WITH RECURRENT GLIOBLASTOMA TREATED WITH BEVACIZUMAB

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INTRODUCTION: Antiangiogenic treatment with the vascular endothelial growth factor-directed antibody Bevacizumab (BEV) is increasingly used in the therapy of recurrent glioblastoma. Assessing response to BEV treatment is nonetheless challenging as the permeability of the blood brain barrier (and hence contrast agent uptake) is reduced through BEV. It is reported, however, that BEV may induce T2-progress by co-opting existing blood vessels, resulting in increased invasiveness of the tumor. This event preceeds recurrent contrast enhancement. Susceptibility-weighted-imaging (SWI) is a new imaging technique that has been shown to be a useful tool in the differential diagnosis of enhancing brain lesions due to the assessment of dotlike hypointensities, so termed susceptibility signals. Here, we analyzed if the increase of SS in the peritumoral area of glioblastoma may predict progressive disease in patients treated with BEV. MATERIAL AND METHODS: 30 patients with histologically proven recurrent glioblastoma were examined at 3 tesla using with SWI (TR:26, TE:19,2, flipangle:15°). All patients received a baseline MRI prior to the first application of BEV followed by 3-monthly f/u MRI. All patients presented T1-progress in one of the subsequent f/u. Two neuroradiologists assessed independently if and in which f/u the number of SS in the peritumoral area increased. RESULTS: 27 of 30 patients showed an increasing number of SS within the peritumoral area. 16 patients presented an increasing number of SS when T1-progress was diagnosed. In 11 patients an increasing number of SS was diagnosed in the precedent f/u before T1-progress was diagnosed. Of those 11 Patients 5 presented T2-progress in the f/u when the number of SS increased. Three Patients did not show any increase in the number of SS at all. DISCUSSION: Our study shows that an increasing number of SS predicts the upcoming T1-progress in patients that are treated with BEV. However the source of the SS is not fully understood yet. One hypothesis is that migrating tumor cells in the invasion front cause microbleeds. In case of standard radiochemotherapy these microbleeds may be accompanied by a vascular reach and leaky tumor boarder, causing contrast enhancing T1-progress. This T1- progress may not be present in case of BEV-therapy due to its antiangiogenic effect. Ultimately the fact that T2-progress was regularly accompanied by SS increase may be caused by the same phenomenon: BEV may suppress blood brain barrier disruption but may not avoid infiltrative tumor progress causing T2-progress as well as SS in the peritumoral area.

O.36. FDG-PET PREDICTS SURVIVAL IN RECURRENT HIGH GRADE GLIOMAS TREATED WITH BEVACIZUMAB AND IRINOTECAN

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Prognosis of recurrent high-grade glioma (HGG) is poor while bevacizumab has been documented in that setting. This study aimed to determine the independent prognostic value of FDG-PET on progression free survival (PFS) and overall survival (OS) of recurrent HGG after combined treatment with bevacizumab and irinotecan, compared to other documented prognostic variables. Twenty-five adult patients with histologically proven HGG were included at recurrence. Brain FDG-PET imaging was performed within 6 weeks of starting chemotherapy with bevacizumab and irinotecan. Response based on MRI was assessed every 2 months according to RANO criterias. Median PFS and OS were 4.0 months (range 0.9-10.4) and 7.2 months (range 1.2-41.7) respectively. At 6 months, PFS and OS rate were 16.0% and 72.0%. FDG uptake was the most powerful predictor of both PFS and OS, using either univariate or multivariate analysis, among all variables tested: histological grade, Karnofsky Performance Status, steroids intake, and number of previous treatments. Moreover, FDG uptake was also prognostic of response to bevacizumab based therapy. This study provides the first evidence that pre-treatment FDG-PET can serve as an imaging biomarker in recurrent HGG for predicting survival following antiangiogenic therapy with bevacizumab.

O.37. CHARACTERIZATION OF THE INFLAMMATORY RESPONSE TO SOLID CANCER METASTASES IN THE HUMAN BRAIN

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BACKGROUND: New immunomodulatroy agents, like ipilimumab, showed promising activity in brain metastases (BM). However, little is known about the inflammatory response in BM and new insights are needed to further guide the development of treatment strategies. METHODS: We investigated 17 human autoptic tissue specimens of BM from breast cancer (n = 3), non-small cell lung cancer (NSCLC; n = 5), small cell lung cancer (SCLC; n = 3) and melanoma (n = 6). Immunohistochemical staining for a comprehensive panel of 21 inflammation-associated markers was performed. Results were quantified by manual counting of the various cell populations in three areas of 0.5 mm2 (intratumoral, peritumoral, control region). RESULTS: Profound microglia activation with marked peritumoral accumulation and some intratumoral infiltration of HLA-DR-positive microglia/macrophages was found. A high proportion of these cells showed strong immunoreactivity for phagocytosis associated markers and MHC class 1, while a smaller subgroup of cells expressed molecules involved in radical production (inducible nitric oxide synthase or NADPH oxidases). Only few B- and T-lymphocytes were observed in and around BM. The number of CD8-positive T-cells was not correlated to MHC class 1 expression on microglia/macrophages or tumor cells. Melanoma BM had significantly less dense peritumoral microglia infiltrates than NSCLC BM. The inflammatory pattern was independent from treatment of patients with glucocorticoids or radiation. CONCLUSIONS: Inflammatory reaction to BM is mainly characterized by activation of microglia/macrophages and shows pronounced upregulation of markers involved in phagocytosis, but seems to be insufficient in activating T-cell response. Treatment strategies aimed at activating specific immunity may potentiate immune attack on tumor cells.

O.38. TARGETING REFRACTORY PILOCYTIC ASTROCYTOMAS BY CELECOXIB AND FLUVASTATIN ASSOCIATION

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Pilocytic astrocytomas (PA) are grade I gliomas that occur predominantly in childhood. These tumors affect preferentially the cerebellum and the optic pathway, especially the hypothalamo-chiasmatic (H/C) region. Cerebellar tumors have a benign clinical course whereas H/C PA display a worse

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prognosis. Conventional chemotherapy is not effective and some side effects are known. Our aim was to understand the molecular bases responsible for the aggressive behavior of H/C PA, as a prerequisite to set up new molecular targeted therapies. Previously, our comparative study of transcriptional profiles of H/C PA and cerebellar PA has shown expression of genes coding for molecules considered as potential therapeutic targets in the treatment of H/C PA: CRK, ICAM-1, IQGAP1/Cdc42 and CD36. These genes are known to be involved in the processes of migration, adhesion and cell proliferation and they are known targets for fluvastatin and/or celecoxib. Therefore, the study of these two drugs in PA is particularly attractive. Celecoxib is a non-steroidal anti-inflammatory drug (NSAID) and a highly selective inhibitor of cyclo-oxygenase-2 (COX-2), which is a rate-limiting enzyme in the prostaglandin synthesis pathway. Fluvastatin is a member of the statins family and is commonly used for the treatment of patients with hypercholesterolaemia. We have searched, by RT-QPCR, for the expression of these 5 genes known or suspected to be Fluvastatin and/or celecoxib targets in a cohort of 51 PA vs 10 glioblastomas (GBM). We demonstrated that CRK, CD36, IQGAP1/Cdc42, and ICAM-1 were significantly over-expressed in the 17 optic pathway PA vs the 27 cerebellar PA. Moreover, CRK and ICAM-1 were significantly over-expressed in PA vs GBM. To go further, we used 2 PA cell lines, established in our laboratory, and 2 glioblastoma cell lines (U87-MG and U118) and determined by the MTT assay the IC50 values for celecoxib and fluvastatin. We showed that all PA and glioblastoma cell lines were sensitive to the drugs but the sensitivity was greater for the PA cell lines. As a proof of concept, and after the information and approbation of the parents, we have treated a 4 years old child suffering from refractory H/C PA with the combination of Fluvastatin/Celecoxib. The treatment was well tolerated and lead to a stabilization of the clinical symptoms and to a decrease in the contrast-enhancing part of the tumour. Altogether, these results open new insights on the treatment of H/C PA.

GLIOMA-CLINICAL STUDIES AND NEUROIMAGING

O.39. DOSE-DENSE TEMOZOLOMIDE AS INITIAL TREATMENT FOR PROGRESSIVE LOW GRADE OLIGODENDROGLIAL TUMORS: A MULTICENTER PHASE II STUDY OF THE AINO (ITALIAN ASSOCIATION OF NEURO-ONCOLOGY)

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BACKGROUND: Standard temozolomide has been shown to be active in progressive low grade gliomas after surgery, whereas few data are available on the impact of dose dense regimens. Thus, we developed a phase II single arm multicenter study to evaluate the efficacy and toxicity of a regimen of dose dense temozolomide as an upfront treatment for low grade oligodendroglial tumors in progression after surgery. PATIENTS AND METHODS: The inclusion criteria of the study were as follows: 1)biopsy-proven supratentorial WHO grade II oligodendroglioma and oligoastrocytoma; 2)progressive disease, clinically (uncontrolled epileptic seizures) or radiologically; 3)measurable disease on MRI (at least 1 cm diameter); 4)age $\geq$18 years; 5)Karnofsky Performance Status $\geq$70. Temozolomide was administered at 150mg/m^2 1 week on/1 week off up to a maximum of 18 cycles or unacceptable toxicity. The primary end-point was response rate (RR) according to RANO criteria, whereas secondary end-points were clinical benefit in terms of a significant reduction of epileptic seizures ($\geq$50%), progression-free survival (PFS), quality of life and toxicity. RESULTS: From January 2005 until December 2010 60 patients (median age 39 and median KPS 80) have been accrued and are evaluable for response. Response rates on T2/FLAIR images were as follows: CR 0/60, PR 21/60 (35%) and MR 14/60 (23%) for an overall response rate of 58%. SD and PD were 21/60 (35%) and 4/60 (7%), respectively. A significant reduction of epileptic seizures was observed in 29/34 patients (85%). As for toxicity 5/60 (8%) patients stopped the treatment for lymphopenia grade IV, whereas 11/31 patients (35%) were switched to the standard regimen of temozolomide. PET with methionine was added to MRI in 17 patients: in 10/17 (59%) a disappearance or a significant reduction of uptake was observed, being the reduction of seizures better correlated with the response on PET rather than that on MRI. A preliminary analysis showed that 1p/19q codeletion and MGMT methylation were not associated with either the response or the clinical benefit. IDH1 mutation analysis is ongoing. Thirty-three (55%) patients are still free of tumor progression, with a median follow up of 33 months (range 15 months-7 years). CONCLUSIONS: Compared to historical controls, receiving the standard regimen, dose-dense TMZ seems more active in terms of clinical benefit, but not in terms of MRI response. Myelotoxicity is a real concern. Randomized studies are needed.

O.40. HOT-SPOTS IN DYNAMIC ^{18}FET PET ARE ASSOCIATED WITH UNFAVORABLE OUTCOME IN PATIENTS WITH SUSPECTED WHO GRADE II GLIOMA

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PURPOSE: Three different uptake patterns of O-(2-[(18)F]fluoroethyl)-l-tyrosine (^{18}FET) have been shown to occur in patients with suspected WHO II glioma after dynamic PET evaluation: 1; a constantly increasing uptake throughout the entire tumor volume indicative for a grade II glioma. 2; an early peak of uptake with following decline throughout the entire tumor volume indicative for a malignant glioma. 3; a heterogeneous uptake exhibiting both low- and high-grade characteristics (HOT SPOT) at different sites of the tumor. The prognostic impact of these findings remains unclear so far. For clarification the following prospective study (2006-2010) was conducted. METHODS: Adult patients with a magnetic resonance imaging based suspicion of a so far untreated grade II glioma were considered eligible. Date of last follow-up was October 2011. Informed consent was available for all patients. Dynamic FET PET evaluation was performed according to the protocol of Poepperl et al (2007). All patients underwent PET-guided stereotactic biopsy. Progression free survival (PFS) was estimated with the Kaplan Meier method. RESULTS: Ninety-eight patients (f/m 56/42, median age 45yrs) were included. Median follow-up was 16 months. Histological evaluation revealed 53 grade II and 45 high-grade gliomas. Tumor progression was noted in 31 patients. The diagnostic sensitivity and specificity of FET PET was 89% and 87%. Homogeneous low-grade, homogeneous high-grade, and heterogeneous kinetics were seen in 52, 27, and 19 patients, respectively. The size of the HOT SPOT in the heterogeneous group ranged from 2 to 90% of the entire tumor volume. One-year PFS for patients exhibiting homogeneous low-grade, homogeneous high-grade, and heterogeneous kinetics was 86%, 63%, and 87%, however, two-year PFS was 78%, 35%, and 26%, respectively ($p = 0.002$). Patients exhibiting heterogeneous kinetics did no better than those with homogeneous malignant kinetics ($p > 0.05$). The size of the HOT SPOT did not gain prognostic relevance. CONCLUSIONS: Consideration of HOT SPOT volumes within suspected grade II glioma is essential for histological and prognostic evaluation. Failure to detect these sometimes small malignant foci either by microsurgery or biopsy could easily lead to both undergrading and undertreatment.

O.41. 11C-METHIONINE PET COMBINED WITH ADVANCED MRI FOR THE PREOPERATIVE EVALUATION OF SUSPECTED DIFFUSE LOW-GRADE GLIOMAS

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PURPOSE: To evaluate positron emission tomography (PET) with the tracer 11C-methionine (MET) combined with perfusion- and diffusion MRI (pMRI and dMRI) for the preoperative evaluation of patients with suspected diffuse low-grade gliomas (DLGG). MATERIALS AND METHODS: In this prospective study with institutional review board approval, 25 patients with suspected DLGG in cortical structures ($n = 24$) were examined with 11C-methionine PET (MET PET), pMRI and dMRI. The hot spot (HS) in the tumor, i.e. the area with highest MET uptake, was used as a reference region for evaluating maximum relative cerebral blood volume (rCBVmax) and minimum apparent diffusion coefficient values (ADCmin) by MRI. The concordance between MET PET, pMRI and dMRI, as single parameters and combined, was assessed with respect to histological tumor diagnosis, which was available for 18 patients. RESULTS: In all but one patient tumor diagnosis was confirmed. The region showing highest rCBVmax corresponded with the HS region identified by MET PET in all cases, and a positive correlation between MET uptake and rCBVmax was found (Spearman: $r = 0.67$, $P < 0.0001$). The concordance between MET uptake and rCBVmax in predicting malignancy grade of gliomas was 67%. MET uptake in the HS was inversely correlated with ADCmin values measured in this region (Spearman: $r = -0.54$, $p < 0.005$). CONCLUSION: MET PET combined with advanced MRI facilitates the identification of specific regions of interest for histological tumor diagnosis

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and thereby provides a powerful tool in the preoperative evaluation of DLGG.

O.42. LONG TERM FOLLOW-UP RESULTS OF EORTC 26951: A RANDOMIZED PHASE III STUDY ON ADJUVANT PCV CHEMOTHERAPY IN ANAPLASTIC OLIGODENDROGLIAL TUMORS - A REPORT OF THE EORTC BRAIN TUMOR GROUP

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BACKGROUND: Anaplastic oligodendroglial tumors (AOD) are chemotherapy sensitive tumors especially if 1p/19q co-deleted. Between 1995 and 2002 the EORTC Brain Tumor Group conducted a prospective phase III study on adjuvant procarbazine, CCNU and vincristine (PCV) chemotherapy in AOD. We now present long term follow-up. MATERIAL AND METHODS: Patients (pts) were eligible if locally diagnosed with a newly diagnosed AOD. Pts were randomized between radiotherapy (RT, 33 x 1.8 Gy) and the same RT followed by 6 cycles standard PCV (RT/PCV). Primary endpoints were overall survival (OS) and progression free survival (PFS). 1p/19q status, *IDH* status and *MGMT* promoter methylation were determined in 300, 167 and 186 pts respectively. RESULTS: Between 1996 and 2002 368 pts were included. At the time of analysis 281 pts (76.4%) had died. Median PFS after RT/PCV was significantly longer compared to RT alone (24.3 months versus (vs) 13.21 months, Hazard Ratio (HR) 0.66, [95% confidence interval (95% CI) 0.52, 0.83]. More RT arm patients received chemotherapy at progression (75% vs 53%). Median OS was also significantly prolonged in the RT/PCV arm (42.3 months vs 30.6 months for the RT arm, HR 0.75 [95% CI 0.60, 0.95]. 1p/19q co-deleted patients ($n = 76$) treated with RT/PCV had improved OS compared to RT alone pts (median OS not reached vs 113 months; HR 0.54, $p = 0.0487$). In the 224 patients without 1p/19q co-deletion the difference in OS was non-significant (OS RT/PCV arm 25 months vs 22 months in the RT arm, HR 0.82, $p = 0.18$; test for interaction $p = 0.22$). There was a slight trend towards improved outcome in *MGMT* methylated and *IDH* mutated tumors versus unmethylated and *IDH* wild type tumors. CONCLUSION: The addition of PCV to RT increases PFS and OS in AOD. Pts with 1p/19q co-deletion appear to benefit most, with a trend for improved OS in RT/PCV treated pts with *MGMT* promoter methylation and *IDH* mutations.

O.43. *MGMT* PROMOTER METHYLATION PREDICTS BENEFIT FROM TEMOZOLOMIDE *VERSUS* RADIOTHERAPY IN MALIGNANT ASTROCYTOMAS IN THE ELDERLY: THE NOA-08 TRIAL

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BACKGROUND: The current standard of care in the increasing population of patients with glioblastoma or anaplastic astrocytoma is resection or biopsy followed by involved-field radiotherapy (RT). The role of primary chemotherapy is not defined. The NOA-08 trial tested the hypothesis that dose-dense temozolomide (TMZ) is not inferior to RT in patients with newly diagnosed anaplastic astrocytoma or glioblastoma aged 66 or more. METHODS: Patients ($n = 412$; 39 anaplastic astrocytoma, 373 glioblastoma) > 65 years with a Karnofsky performance score > 60 were randomized to receive RT or TMZ (*one week on one week off*). The primary endpoint was overall survival (OS). RESULTS: Patient characteristics in the intention-to-treat population [$n = 373$ (178 patients RT, 195 patients TMZ)] were balanced. All histologic diagnoses were centrally confirmed. Median OS [hazard ratio, HR, =1.09 (95% confidence interval, CI: 0.84-1.42)] and event-free survival (EFS) [HR = 1.15 (0.92-1.43)] of TMZ *versus* RT did not differ between both arms. Non-inferiority of TMZ compared with RT was significant ($p = 0.033$). Extent of resection, but not age or diagnosis of anaplastic astrocytoma, were associated with prolonged EFS and OS. O^6-*methylguanine DNA-methyltransferase* (*MGMT*) promoter methylation in tumor tissue was associated with prolonged OS [HR = 0.67 (0.38-1.29)]. Patients with *MGMT* promoter methylation had longer EFS when treated with TMZ (8.4 months [5.5-11.7] *versus* RT (4.6 [4.2-5] months) whereas patients without *MGMT* promoter methylation had longer EFS when treated with RT (4.6 [3.7-6.3] *versus* 3.3 [3-3.5] months). This effect persisted for OS. CONCLUSIONS: NOA-08 demonstrates the non-inferiority of TMZ compared with RT in the treatment of elderly patients with malignant astrocytoma. *MGMT* promoter methylation is a strong predictive biomarker for the choice between RT and TMZ.

O.44. ENZYME INDUCING ANTIEPILEPTIC DRUGS AND SURVIVAL OF PATIENTS WITH RECURRENT MALIGNANT GLIOMA

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OBJECTIVES: This analysis was performed to look for support for the proposition that treatment with enzyme inducing antiepileptic drugs (EIAED) can modulate the effectiveness of chemotherapy in patients with recurrent malignant glioma when compared to patients treated with non-enzyme inducing antiepileptic drugs including sodium valproate (NEIAED). METHODS: Data from the Medical Research Council trial of temozolomide versus procarbazine, lomustine and vincristine in recurrent high grade glioma (ISCRTN83176944)) were examined to assess the impact of the concurrent use of EIAED or NEIAED and chemotherapy on progression free survival and the incidence of Grade 3 or 4 haematological toxicity or skin rash. Data were available for 430 patients with recurrent malignant glioma previously treated with radiotherapy. There were adequate data on 418/447 patients for the purposes of this analysis. RESULTS: No evidence was found to support a difference in progression free survival (PFS) between patients treated with only EIAED or NEIAED irrespective of which chemotherapeutic agent they were treated with (Median PFS 129 days with EIAED and 145 days with NEIAED $p = 0.537$). There was no evidence to support a difference in the frequency of Grade 3 or 4 haematological toxicity or skin rash between patients treated with EIAED or NEIAED (haematological toxicity 20.5% with EIAED vs 14.5% with NEIAED, $p = 0.277$ and skin rash 6.6% with EIAED vs 4.5% with NEIAED, $p = 0.508$). CONCLUSIONS: Although a survival advantage has been independently reported with both EIAED and sodium valproate, neither of these findings were supported by this analysis. Further dedicated, randomised studies are needed to determine whether EIAED or NEIAED (including sodium valproate) modulate the effectiveness of temozolomide chemoradiation which is now the standard of care for patients with malignant glioma.

O.45. A PHASE II TRIAL, CONCURRENT 3-TIMES DAILY ULTRAFRACTIONATED RADIATION THERAPY AND TEMOZOLOMIDE FOR NEWLY INOPERABLE GLIOBLASTOMA, TEMOFRAC

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BACKGROUND: Ultrafractionation radiation therapy consists in irradiating cells or tumours several times daily, delivering low doses at which hyperradiosensitivity occur. We recently reported the efficiency of

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ultrafractionation radiotherapy regimen in newly inoperable glioblastoma. We are now conducting a phase II clinical trial to determine the effect of a concurrent ultrafractionation regimen and temozolomide for inoperable glioblastoma patients. □ METHODS: A prospective, multicenter, 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 0.75Gy spaced by at least four hours are delivered daily, five days a week for six consecutive weeks for a total of 67.5Gy, and concomitant chemotherapy consisted of temozolomide given at dose of 75mg/m2, 7 days per week during the ultrafractionated radiotherapy. After a 4-week break, chemotherapy is resumed up to 6 cycles of adjuvant temozolomide every 28 days, according to the standard 5-day regimen. Tolerance and toxicity is the primary endpoints; survival and progression- free survival are secondary endpoints. RESULTS: To date 36 patients have been enrolled in this study, 24 men and 12 women, median age 62, median Karnofsky performance status was 80. The concomitant ultrafractionated radiotherapy -temozolomide was been well tolerated; no acute grade 3 and/or 4 CNS toxicity has been observed. Complete response were reported in 3 patients, and stabilisation or minor responses in 8 patients. Two patients progressed during the radiation therapy, and two patients died of pulmonary embolism. Median survival from initial diagnosis was not yet reached. Half of the patients have survived for more than one year. CONCLUSIONS: TEMOFRAC regimen is safe and well tolerated. It may prolong the survival of patients with glioblastoma. Updated definitive results will be presented at the meeting. □

GLIOMA-EXPERIMENTAL & BIOMARKERS

O.46. DNA AND RNA EXPRESSION PROFILING OF SERUM-FREE PRIMARY MALIGNANT GLIOMA CULTURES REVEALS SELECTION FOR EGFR/PTEN ABERRATIONS BUT COVERAGE OF ALL TCGA-DEFINED GENE EXPRESSION SIGNATURES

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INTRODUCTION: Malignant glioma cell culture models based on serum-free bFGF + EGF supplemented (SF) medium, have been reported to closely mirror the phenotype and genotype of primary tumors and have become the designated platform for malignant glioma in vitro research. However, the take rate of obtaining viable and proliferating SF cell cultures varies between laboratories and is below 100%. We hypothesized that SF culture conditions may introduce a selection bias and with the growing incentive to implement these patient-derived culture panels in translational drug screening programs, this potential selection warrants closer analysis. METHODS: In total, 214 malignant glioma samples were dissociated and cultured under SF conditions. Cultures were termed SF+ when propagatable beyond p5 and SF- when this was not the case. Parental tumors of SF+ and SF- cultures were analyzed by gene expression profiling using Illumina DASL arrays. Parental tumors of successful and unsuccessful cultures were also interrogated on SNP6.0 arrays. In addition, multiple passages of SF+ cultures were analyzed by SNP6.0 arrays. RESULTS: The overall success-rate of in vitro propagation was associated with histological grade, with higher grades giving higher take rates. Of the grade III and IV gliomas (n = 181), 83% of samples initially formed spheroids, whereas only 31% were propagated for more than 5 passages (the SF+ group). Hence, a large group of high-grade gliomas (69%), not propagatable beyond p5, were effectively unsuitable for in vitro drug screening (SF-). Gene expression profiling of a panel of SF+ (n = 22) and SF- (n = 20) parental tumors, demonstrated a similar distribution and coverage of all gene expression signatures as defined by the TCGA in both groups. Genotyping of SF+ tumors, however, revealed a selection for chromosome 10p loss (PTEN) and gains of chr.7 (EGFR). This specific pair of copy number alterations (CNAs) was found in 11/11 SF+ tumors and in only 3/16 SF- tumors. SNP analysis of SF cultures and derived xenografts revealed that the driving CNAs found in the parental tumor were retained over multiple passages in culture and in xenografts in mice. CONCLUSIONS: Currently used serum-free culture protocols for malignant glioma introduce a selection bias for high-grade glioma with EGFR/PTEN aberrations. However, within this population of tumors, established expression signatures are all represented in similar frequencies as reported for the complete population.

O.47. DIFFERENTIAL TUMOR-STROMA INTERACTIONS IN GLIOBLASTOMA

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During the last decade a major role emerged for the intricate relationship between tumor development and microenvironment. We have previously developed a rat glioblastoma (GBM) xenograft model which recapitulates two major characteristics of human GBM: tumor cell infiltration and angiogenesis. In rodent xenografts, the human GBM adapts to the new microenvironment and develops more aggressive tumors after serial transplantation of primary tumor spheroids. Here we adapted the model to GFP expressing immunodeficient mice, where a decrease of survival after serial transplantation was also observed. While the invasive features were also conserved in mice, no typical angiogenesis with microvascular proliferation was detected contrary to the rat model. Different types of tumor vasculature could be observed in mice, including vessels with abnormal morphology and an increase in macrovessels compared to normal brain tissue. To investigate the reciprocal tumor-stroma interaction, tumor and stromal cells were isolated by fluorescence activated cell sorting (FACS) from non-angiogenic highly infiltrative xenografts (invasive phenotype), and from less infiltrative xenografts displaying abnormal vascular elements (vascular phenotype). While both stromal cell populations promoted tumor cell migration, only the stromal cells from the vascular phenotype promoted tube formation in endothelial cells. Interestingly the stromal cells also differentially induced tumor spheroid growth. Using the novel fluorescent xenograft mouse model we were able to identify stromal cell properties based on differential tumor phenotypes. While this model is very useful to distinguish between tumor and stromal cells and to study the infiltrative features of GBM, the xenograft rat model is recommended to study angiogenesis.

O.48. THREE DIMENSIONAL *IN VITRO* CULTURE STIMULATES VASCULOGENIC MIMICRY AND RE-CAPITULATES KEY FEATURES OF HIGH GRADE BRAIN TUMOURS.

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INTRODUCTION: Angiogenesis is of critical importance in the rapid growth of high grade brain tumours, with studies suggesting tumour differentiation into functional vasculature is possible. Conventional monolayer two dimensional (2D) is a highly reductionist model with a lack of the three dimensional (3D) framework and aberrant extracellular matrix deposition. Using a novel 3D culture system we demonstrate upregulation of angiogenic pathways and exhibition of vessel like qualities by adult and paediatric high grade brain tumour cells (so called vasculogenic mimicry) with gene expression and drug sensitivity closer to primary tumours than 2D cell culture. METHODS: The Rotary Cell Culture System (RCCS) was used to cultivate 0.2-0.8cm^3 aggregates of high grade brain tumour cell lines, an endothelial cell line and primary tumour explants. Identical media and other culture parameters to 2D culture were utilised. Genome wide gene expression analysis comparing primary tumour with 2D and 3D culture was performed using the Affymetrix U133plus2 chip and Nanostring MicroRNA chip. Expression of 84 angiogenesis and 84 ECM related genes was assessed by RT-PCR. Immunohistochemistry was performed against vessel related antigens and components of angiogenic pathways. The hypoxyprobe system was utilized to assess hypoxia. Magic angle spinning magnetic resonance spectroscopy was performed to establish metabolic profiles. Drug testing was performed using the HDAC inhibitor vorinostat. Statistical comparisons were made between cell lines cultured in conventional 2D monolayers and the same cell lines cultured in the RCCS. RESULTS: Tumour aggregates possess a complex heterogeneous structure with distinct proliferating, hypoxic and necrotic regions, replicating primary tumour. Endothelial antigens such as CD105 and CD31 are expressed by tumour cells. Genome wide analysis and rt-PCR identified multiple pro-angiogenic genes upregulated in 3D culture with gene expression shifted towards that of primary tumour. Metabolic profiles demonstrated significant differences including elevated lipids in 3D compared to 2D cultures. Tumour drug sensitivity is significantly reduced in 3D culture, more closely replicating drug sensitivities seen *in vivo*. CONCLUSIONS: We demonstrate that 3D culture recapitulates many key

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characteristics of primary brain tumours. Our findings contribute to understanding the angiogenic process in high grade brain tumours and mechanisms of resistance to current anti-angiogenic therapies. The 3D culture system permits evaluation of next-generation anti-angiogenic agents in a pathophysiologically relevant context.

O.49. PROGNOSTIC VALUE OF CD109+ CIRCULATING ENDOTHELIAL CELLS IN GLIOBLASTOMA PATIENTS TREATED WITH BEVACIZUMAB

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BACKGROUD: Bevacizumab, a monoclonal antibody targeting the vascular endothelial growth factor (VEGF), can prolong survival of patients with recurrent glioblastomas (GB). However, predictive markers to select patients who may benefit from treatment are still lacking. OBJECTIVE: To correlate conventional MRI signs and circulating endothelial cells (CECs) and progenitors (CEPs) with clinical outcome in a prospective cohort of recurrent GB patients treated with bevacizumab (10 mg/kg, i.v.) and irinotecan (125 or 340 mg/m^2, depending on the concomitant use of enzyme-inducing antiepileptic drugs) every 2 weeks. METHODS: We treated 74 patients with recurrent GB: median KPS was 70 (50-100), whereas median age was 52.5 (15-76). Radiological follow up was performed every 8 weeks together with CECs and CEPs evaluation by flow cytometry. The log rank test was used to test for differences in progression or survival among patients with different clinical, radiological or biological parameters and Wilcoxon rank sum test for changes among circulating endothelial cells during treatment. RESULTS: Safety data obtained in our population are comparable to those reported in literature. Median OS and PFS were 29 and 18 weeks, respectively. PFS at 6 and 12 months were 34% and 12%. OS at 6 and 12 months were 55% and 22%, respectively. Patients with distant intracerebral disease at baseline MRI had shorter PFS (9 vs 26 weeks, $p = 0.0001$) and OS (19 vs 38 weeks, $p = 0.0001$). Furthermore, patients without dexamethasone treatment at baseline had longer PFS (29 vs 10 weeks, $p = 0.01$) and OS (39 vs 23 weeks, $p = 0.009$). Baseline CD109+ CECs over 41.1 cells/ml (1st quartile) were associated with longer PFS (9 vs 20 weeks, $p = 0.02$) and OS (22 vs 31 weeks, $p = 0.04$). Patients who progressed after 18 weeks of therapy or more ($n = 26$) had baseline levels of CD109+ CECs significantly higher than others ($p = 0.01$). CONCLUSIONS: Baseline CD109+ CECs may be promising markers for the selection of GB patients who could benefit from bevacizumab. These observations encourage the study of the predictive value of CECs on larger number of patients.

O.50. TGF-β MEDIATES THE HOMING OF BONE MARROW-DERIVED HUMAN MESENCHYMAL STEM CELLS TO GLIOMA STEM CELLS

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Although studies have shown that intravascularly delivered bone marrow human mesenchymal stem cells (hMSCs) home to commercially available glioma cell lines, no study has addressed whether hMSCs home to human glioma stem cells (GSCs), which are the glioma-initiating cells responsible for treatment failures. Consequently, we determined whether hMSCs were capable of homing to five GSC neurosphere lines (GSC11, GSC17, GSC 229, GSC268, GSC274) obtained from fresh human surgical specimens. Xenografts of each of these GSCs were established in the frontal lobes of nude mice, and gfp-labeled hMSCs were injected into the carotid artery. Fluorescent microscopy showed that hMSCs were capable of homing to xenografts of GSC17, GSC268, and GSC274, but not to xenografts GSC11 and GSC229, indicating that there is heterogeneity in the capacity of hMSCs to target GSCs *in vivo*. Because our previous studies suggested that TGF-β may mediate hMSC homing to gliomas, we asked whether there was a correlation between TGF-β expression and hMSC homing in our 5 GSC xenografts. Immunohistochemical staining for TGF-β demonstrated that all three GSC xenografts that attracted hMSCs expressed high levels of TGF-β, whereas TGF-β was not detectable in the two GSC tumors that did not attract hMSCs. To establish a causal role of TGF-β, we stably over-expressed TGF-β in GSC229, thereby converting a GSC that does not produce TGF-β into one that does. Intracarotid injections of hMSCs to mice harboring xenografts of GSC229-vector or GSC229-TGFβ showed that hMSCs homed only to GSC229-TGFβ xenografts, whereas GSC229-vector xenografts remained unable to attract hMSCs. To further define the role of TGF-β, TGFβ Receptor II was knocked down in hMSCs (hMSCs-TGFβRII-kd) and these hMSCs were injected into the carotid arteries of mice bearing intracranial xenografts of GSC17 (high TGF-β). Whereas hMSCs localized to GSC17, hMSC-TGFβRII-kd were unable to home to GSC17. Finally, we tested if hMSCs carrying the oncolytic adenoviruses, Delta-24-RGD (hMSCs-Delta-24-RGD), were efficacious against GSCs expressing high levels of TGF-β. Compared wtih controls, hMSCs-Delta-24-RGD significantly prolonged the survival of mice bearing GSC17 intracranial xenografts. In contrast, hMSCs carrying Delta-24-RGD, but in which TGFβRII was knocked down, were unable to alter the survival of the mice. We conclude that hMSCs home to many, but not all GSCs, and that TGF-β may predict patients in whom BM-hMSC delivery will be most effective.

O.51. ABERRANT EXPRESSION OF LOW MOLECULAR WEIGHT PROTEINS ASSOCIATED WITH RESPONSE TO CONVENTIONAL CONCURRENT CHEMORADIOTHERAPY TREATMENT AND OVERALL SURVIVAL

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Despite undeniable progress in the care and treatment of primary brain tumours, for most patients diagnosed with GBM prognosis is poor and few survive more than 3 years. The standard treatment for newly diagnosed GBM involves maximal surgical resection followed by treatment with temozolomide (TMZ) combined with radiotherapy (RT) (chemoradiotherapy), however essentially all tumours recur after this initial therapy and response is highly varied. We collected frozen tumour tissue from patients ($n = 42$) prior to treatment with chemoradiotherapy and examined the differential expression of low molecular weight proteins in these specimens when grouped according to their response to treatment. Response was defined by progression free survival (PFS $\geq$ 6 months; PFS6) and survival greater than the total median. SELDI-TOF MS technology was used to detect differentially expressed small molecular weight proteins between patient groups. Data obtained from four chemically modified ProteinChip surfaces indicated at least 39 peaks significantly different proteins. Binary logistic regression (BLR) models were used and three proteins (10.2, 12.3, 10.8 kDa) were identified in the response group with strong prediction capacity. These biomarker candidates, 10.2, 12.3 and 10.8 were identified to be Alpha Defensin 3 (DEFA3), Macrophage Inhibitory Factor (MIF) and Calgranulin A (S100A8), respectively. All three proteins were up-regulated in patients showing poor response and survival after treatment with chemoradiotherapy. Interestingly, all three proteins play a role in the mediating inflammation and are derived from non-neoplastic cells including neutrophils and macrophages (as opposed to restricted expression in the tumour cells) Protein expression of all three candidates were confirmed in an independent cohort of glioblastoma ($n = 65$, uniformly treated with chemoradiotherapy). DEFA3 and S100A8 were expressed in tumour-infiltrating granulocytes, predominantly in neutrophils. Nuclear and cytoplasmic localisation of MIF was detected in tumour cells. High MIF immunostaining was also specific to tumour cells localised within the regions of palisading necrosis. To conclude, we demonstrated a unique multimarker model to differentiate responders from non-responders with high predictability. Manipulation of these proteins *in vitro* and *in vivo* will determine the precise role that these biomarkers play in mediating sensitivity to the standard therapy.

O.52. IDENTIFICATION OF NOVEL GENOMIC BIOMARKERS IN LOW-GRADE GLIOMAS WITHOUT 1P19Q CODELETION

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Diffuse low-grade gliomas (LGG) (WHO grade II) are a very heterogeneous group of glial tumors in terms of pathological features and clinical outcome. In addition, the diagnosis of LGG, based on morphological criteria, is challenging in daily practice. Interestingly, over the last years, several molecular markers with clinical significance have been identified in LGG. The most relevant molecular biomarkers are: (i) 1p19q codeletion associated with

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oligodendroglial phenotype and better prognosis; (ii) isocitrate dehydrogenase (IDH) 1 and 2 mutations associated with better prognosis; (iii) TP53 mutations associated with astrocytic phenotype and (iv) MGMT promoter methylation associated with better prognosis. In order to identify new genomic biomarkers in LGG we have performed a genome-wide analysis using BAC-array based comparative genomic hybridization in a retrospective series of 152 LGG. Then, we have correlated genomic profile of tumors with clinical characteristics of patients in one hand and pathological features, TP53 expression, IDH mutation status and MGMT promoter methylation status of tumors in the other hand. The study population included 152 patients with LGG (75 oligodendrogliomas, 53 oligoastrocytomas and 24 astrocytomas). Our study showed that LGG gliomas are heterogeneous at genomic level identifying five major genomic groups in non 1p19q codeleted tumors: (i) 11p loss, (ii) monosomy 19 (iii) trisomy 7, (iv) trisomy 19 and (v) unclassified. As expected, 1p/19q codeletion and IDH mutation have favorable prognostic value. Interestingly, tumors harboring 11p loss are almost exclusively low-grade astrocytomas and express high level of TP53. Surprisingly, IDH mutated tumors exhibiting chromosome 19 monosomy have worse prognosis similar to IDH wild-type LGG. In summary, our study identified novel genomic entities and biomarkers in LGG. Indeed, chromosome 11p loss was associated with astrocytic phenotype. In addition, chromosome 19 monosomy is associated with poor prognosis in IDH mutated tumors reducing the favorable prognostic value of the positive prognostic value of IDH mutation in LGG. Further prospective studies are warranted to specify our findings.

O.53. IDENTIFICATION OF A GLIOBLASTOMA STEM CELL SPECIFIC COMMUNICATION MECHANISM THAT DRIVES MALIGNANCY AND IS AMENABLE FOR THERAPEUTIC TARGETING

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Notch signaling is a paradigm for cell communication in normal and cancer stem cells but the development of therapeutic strategies targeting pathways shared by both normal and cancer stem cells is not optimal. To identify tumor specific cell communication mechanisms, we conducted a high throughput flow cytometry screen of primary tumor cells from Glioblastoma Multiforme (GBM). Our screen identified a unique GBM progenitor cell antigen (GPCA2) expressed in a fraction of GBM cells. GPCA2 has been detected in breast cancer where it correlates with poor survival and is linked to cell survival via integrin receptors, which we previously showed to be critical in GBM stem cell (GSC) maintenance in the perivascular niche (Lathia et al., Cell Stem Cell 2010). To evaluate the relevance of GPCA2 in brain tumors, we analyzed several brain tumor types (Oligodendroglioma, Grade III Astrocytoma, Grade IV GBM) and found that GPCA2 expression increased with tumor malignancy. GPCA2 expression was informative to predict patient survival, with elevated GPCA2 levels correlated with poor patient prognosis. GPCA2 levels were significantly higher in GBM tissue as compared with normal neural progenitor cells (NPCs) and GPCA2 deficient mice showed no growth defects or differences in NPC compartments (subventricular zone, dentate gyrus), confirming the tumor specific expression of GPCA2. Histological analysis of GBM tissue revealed GPCA2 positive cells in the perivascular compartment, a known GSC niche. GSCs enriched from human GBM tumors showed elevated protein expression of GPCA2 as compared to matched non-GSCs. We evaluated GPCA2 expression with integrin alpha 6, a known GSC integrin expressed in the perivascular niche, and found above 70% co-expression. To interrogate the functional consequence of GPCA2 inhibition, we utilized a blocking antibody and found an increase in cell death and decrease in growth and self-renewal of GSCs in a concentration dependent manner. Matched non-GSCs and NPCs were not adversely impacted by the GPCA2 blocking antibody, suggesting GSC specific role for GPCA2 in promoting growth and self-renewal. To confirm our GPCA2 targeting results using a genetic approach, we utilized shRNA and found decreased GSC growth and self-renewal using 2 separate shRNA constructs against GPCA2. Protein analysis of GSCs with attenuated GPCA2 showed decreased levels of GSC self-renewal specific pathways (STAT3, Sox2, Olig2) and concomitant decreases in integrin alpha 6. GSCs may utilize unique communication pathways to promote malignancy and our studies have identified one such mechanism that is amenable for targeting in GBM.

LATE-BREAKING ABSTRACTS

LB.01. Hotspot mutations in H3F3A and IDH1 define distinct epigenetic and biological subgroups of glioblastoma

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Glioblastoma (GBM) is a brain tumor type that carries a universally dismal prognosis and displays considerable heterogeneity. We have recently identified recurrent *H3F3A* mutations affecting two critical amino acids (K27 and G34) of histone H3.3 in one-third of pediatric GBM. In the present study, we further investigate the heterogeneity of glioblastoma across the entire age spectrum and elucidate the impact of *H3F3A* mutations on the GBM epigenome.

We used an integrative approach based on epigenetic, copy-number, expression, and genetic analyses to investigate the heterogeneity of glioblastoma across all age groups. We investigated a cohort of GBMs from children ($n = 59$) and adult patients ($n = 77$) for genome-wide DNA methylation patterns using the Illumina 450k methylation array, and complemented our data with unpublished profiles of 74 adult GBM samples generated by The Cancer Genome Atlas (TCGA) Consortium. Tumors were further characterized for their mutational status, gene expression, and copy-number profiles. A total number of 460 GBM samples were screened for mutations in *H3F3A* and *IDH1*. Differential protein expression of OLIG2, FOXG1, and mutated IDH1 was assessed by immunohistochemistry using a tissue microarray representing 143 pediatric GBM patients. Molecular findings were correlated to available clinical patient data.

Each *H3F3A* mutation defines an epigenetic subgroup of GBM with a distinct global DNA methylation pattern, and both are mutually exclusive with *IDH1* mutations, characterizing a CpG-Island Methylator Phenotype (CIMP). Three further epigenetic subgroups were enriched for hallmark genetic events of adult GBM (amplifications of *PDGFRA* or *EGFR*, homozygous deletions of *CDKN2A*) and/or described transcriptomic signatures. Epigenomic GBM subgroups correlate with key clinical parameters such as patient age and survival. We also demonstrate that the two *H3F3A* mutations give rise to GBMs in separate anatomic compartments, with differential regulation of *OLIG1*, *OLIG2* and *FOXG1*, possibly reflecting different cellular origins. Our findings suggest that approximately 40% of pediatric/young adult GBMs are characterized by disrupted epigenetic regulatory mechanisms, associated with recurrent and mutually exclusive mutations in either *H3F3A* or *IDH1*, and aberrant DNA methylation patterns.

In conclusion, this study describes a number of findings that enhance our understanding of the heterogeneity of GBM, as well as shedding new light on potential cellular origins and oncogenic pathways leading to gliomagenesis. We have identified potential prognostic biomarkers which may be further exploited for molecular diagnostic purposes, and also provided a focus for future work at a basic and translational/targeted therapeutic level, particularly in a pediatric and young adult setting.

LB.02. The soluble form of the tumor suppressor Lrig1 potently inhibits in vivo glioma growth irrespective of EGF receptor status

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Background: Deregulated growth factor signaling is a major driving force in the initiation and progression of glioblastoma. The tumor suppressor and stem cell marker Lrig1 is a negative regulator of the epidermal growth factor receptor (EGFR) family. Here we addressed the therapeutic potential of the soluble form of Lrig1 (sLrig1) in glioblastoma treatment and the mechanism of sLrig1-induced growth inhibition. Methods: Using encapsulated cells, recombinant sLrig1 was locally delivered in orthotopic glioblastoma xenografts generated from freshly isolated patient tumors. The efficacy and mechanism of action of sLrig1 was studied *in vitro* and *in vivo* in glioma

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cells displaying variable expression of wildtype and/or a constitutively active EGFR mutant (EGFRvIII). Results: Continuous interstitial delivery of sLrig1 in genetically diverse patient-derived glioma xenografts led to strong tumor growth inhibition. sLrig1 potently inhibited glioma cell proliferation *in vitro* and tumor growth *in vivo* irrespective of EGFR expression levels. Importantly tumor growth was also suppressed in EGFRvIII driven glioma. Overexpression of sLrig1 in U87 cells induced cell cycle arrest, without affecting EGFR protein level or phosphorylation status. Affected downstream effectors included MAP kinase but not AKT signaling. Conclusions: This is the first report demonstrating that sLrig1 is a potent inhibitor of glioblastoma growth in clinically relevant experimental glioma models and that this effect is largely independent of EGFR status. The potent anti-tumor effect of sLrig1, in combination with cell encapsulation technology for *in situ* delivery holds promise for future treatment of glioblastoma.

POSTER PRESENTATIONS

[Poster numbers marked with * will also be presented orally]

CELL BIOLOGY AND SIGNALLING

P.001. HEAT SHOCK PROTEINS IN BRAIN TUMORS

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OBJECTIVE: Heat shock proteins (HSP) are evolutionary conserved family of proteins that serve as molecular chaperones. HSP are induced by cell stress and have been found highly overexpressed in a wide range of human cancers. We set out to investigate the expression of HSP27, HSP40, HSP60, HSP70, HSP90a, total Akt and phospho Akt in tumor specimens by using multiplex bead array assay. METHODS: We studied the brain tumor specimens from 19 patients that were treated surgically in our institute. Nine patients suffered from glioblastoma, 1 from anaplastic oligoastrocytoma, 6 from typical meningiomas, 1 from atypical meningioma, 1 from acoustic neuroma and 1 from a metastatic brain tumor. RESULTS: There was expression of HSP27 (pSer82), HSP27 (pSer15), HSP40, HSP60, HSP70, HSP90a, Akt (total) and Akt (phospho) in both gliomas and meningiomas. Significant higher levels of HSP70 and a trend towards higher levels of HSP40 was found in meningiomas compared to gliomas. There was a significant positive correlation between HSP27 (pSer82) and HSP27 (pSer15) expression and between HSP90a and both total AKT and AKT (phosphor). A significant positive correlation between HSP27 (pSer82), HSP27 (pSer15) and total AKT was also observed. HSP70 and HSP90 showed a strong parallel expression. CONCLUSION: There was expression of HSP in the brain tumor specimens that were examined. This is the first time in which many different HSP have been studied. Since HSP are an attractive target for anticancer therapy further studies are needed in order to better assess their relationship with tumor aggressiveness and patients' prognosis.

P.002. GINSENOSIDE RG3-INDUCED APOPTOSIS IN THE HUMAN GLIOBLASTOMA U87MG CELLS THROUGH MEK SIGNALING PATHWAY AND REACTIVE OXYGEN SPECIES

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OBJECTIVE: Various components of ginsenoside are expected to have cancer-prevention effect. Among them, ginsenoside Rg3 has been reported to control of anti-cancer activities in the various cancers. However, the effect of Rg3 and its molecular mechanism have been still unclear on the glioblastoma. Therefore, we investigated the effect of Rg3 on human glioblastoma cell line and its regulating signaling molecular mechanism. MATERIALS AND METHODS: U87MG cells (Human glioblastoma cell line) were treated with Rg3, measured cell viability using MTT assay and trypan blue exclusion assay. The apoptotic characteristics were detected by TUNEL assay, flow cytometry analysis and western blotting. The molecular mechanisms were evaluated through pre-treated various inhibitors (MAPKs inhibitors, general caspase inhibitor and antioxidants). RESULTS: Rg3 induced inhibition of cell viability on the U87MG cells in a dose- and time dependent manners. Apoptotic effect determined based on the positive stained cells by TUNEL assay, immunocytochemistry and flow cytochemistry. Rg3-induced apoptosis was associated with MEK signaling pathway and reactive oxygen species. CONCLUSION: These results could suggest that Rg3 induces apoptosis in the U87MG cells and its effect controlled through MEK signaling pathway and reactive oxygen species. Therefore, Rg3 can be an innovative candidate for chemotherapeutic agent for glioblastoma.

P.003. PHENYLACETYLGLUTAMINATE IN COMBINATION WITH PHENYLBUTYRATE EFFECTIVELY INHIBITS GROWTH OF BRAIN TUMOR CELLS *IN VITRO*

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In this study we have investigated the effectiveness of the combination of phenylacetylglutaminate (PG), a naturally occurring metabolite of phenylalanine with phenylbutyrate (PB). PG is used in the formulation of antineoplaston AS2-1 which is a 4:1 mixture of PG with phenylacetate (PN). The FDA granted Orphan Drug designation for Antineoplastons A10 and AS2-1 for the treatment of gliomas, in 2009. Twelve FDA supervised Phase II clinical trials have confirmed anti-tumor efficacy in several types of brain tumor. PB is indicated for the treatment of glioma and acute promyelocytic leukemia. PB has been shown to inhibit histone deacetylase, induce differentiation and apoptosis in cancer cells. Previous studies in our laboratory have shown that the combination of PG and PN acts synergistically to inhibit growth of U87 glioblastoma cells. Another published report has shown that PB induces apoptosis in prostate cancer cells and is more potent than PN. In this study we have examined the effect of the combination of PG with PB on the DAOY cell line. A Human GeneST microarray study will be performed to understand the molecular pathways involved. Our preliminary results indicate that proliferation of DAOY medulloblastoma cells is inhibited by this combination at low concentrations. We have found that PG causes a down-regulation of AKT2 in DAOY cells. PG is not toxic to normal cells whereas PB has dose-limiting neuro-cortical toxicity. PB has been studied previously in combination with other agents such as 13-*cis*-retinoic acid and 5-azacytidine. We describe the novel combination of phenylacetylglutaminate and phenylbutyrate as effective anti-proliferative agents in glioblastoma and medulloblastoma cells.

P.004. PREDICTION OF THERAPY RESPONSE IN SHORT-TERM TREATED PRIMARY TUMOR-INITIATING CELLS IN VITRO

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INTRODUCTION: The increasing knowledge of the pathogenesis of tumor formation and progression in high grade gliomas has led to the development of a novel group of therapeutic agents which includes small molecule kinase inhibitors. These novel agents often directly interfere with growth factor signaling pathways which are upregulated in brain tumors and are supposed to interfere with oncogenesis by influencing autocrine and paracrine mechanisms. However, and despite promising preclinical studies, results of pilot trials have been generally disappointing. One reason may be the enormous molecular and genetic heterogeneity between individual tumors which often contributes to the varied and often poor treatment response. Therefore, it is demanding to correlate individual response to the general susceptibility of a certain tumor entity to certain substances. METHODS: In our preclinical study we examined the effect of the small molecule receptor-tyrosin-kinase (RTK) inhibitor Sunitinib in 18 tumor-initiating cell lines which were derived from 18 sequential patients using a novel approach with the following features: (1) culture under serum-free conditions; (2) short-term culture and treatment; (3) hypothesis-free evaluation of a response signature by microarray. Cells were treated with Sunitinib or DMSO (control) alone or together with VEGF-A/PDGF-AB for 6 hours. In parallel, the activation and inhibition of signaling molecules downstream of these growth factors receptor tyrosine kinases (RTK) were evaluated by Western-Blot. The treatment response was analyzed by migration and proliferation assays. RESULTS: We observed a heterogeneous pattern of Erk1/2-, AKT-, and STAT3 activation by VEGFA/PDGF-AB as well as inhibition by Sunitinib in all cell lines tested. We found that Sunitinib reduces the migration and proliferation rates of most cell lines tested although sensitivities were distinct. We

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are now on our way to define a molecular signature that predicts treatment response in vitro by correlating the microarray data with the results of our functional studies. DISCUSSION: So far our data clearly demonstrate the heterogeneity of treatment response both on a molecular and functional level. These data underline the importance to preselect patients for clinical trials. We mandate that the concept of a personalized treatment requires an in vitro drug testing tool that enables the prediction of therapy response within a single short-term assay.

P.005. MOLECULAR MECHANISMS UNDERLYING THE ANTITUMOR EFFECT OF FASUDIL ON GLIOBLASTOMA CELLS

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BACKGROUND: Glioblastoma is the most common and aggressive form of malignant glioma and is very difficult to treat successfully. Controlling glioblastoma cell invasion and angiogenesis is essential to improve the prognosis of glioblastoma patients. Constitutive activation of Rho and its downstream target Rho-kinase (ROCK) are crucial for tumor progression. ROCK could be an important pharmacological target for the control of tumor progression. METHODS: The anti-tumor effect of the ROCK inhibitor fasudil on two glioblastoma cells and the molecular mechanisms underlying this effect were investigated. RESULTS: Fasudil suppressed the proliferation of glioblastoma cells and human brain microvascular endothelial cells (HBMECs) at higher concentration. Fasudil also inhibited the migration of HBMECs, and suppressed both the invasion of glioblastoma cells and tumor-induced angiogenesis. Molecular-based studies demonstrated that 20 μM fasudil suppressed gene and protein expression of angiogenic factors. Furthermore, fasudil reduced the phosphorylation of ERK1/2 and DNA binding activity of activator protein-1, suggesting that the anti-tumor effect of fasudil may be mediated by the inhibition of ROCK and the MEK/ERK pathway. An *in vivo* intracerebral human glioblastoma xenograft mouse model demonstrated that fasudil suppressed neovascularity and tumor growth. CONCLUSION: The results of the present study suggest that fasudil is a potential new therapy against glioblastomas.

P.006. BRAIN TUMOR TISSUE OBTAINED BY ULTRASONIC ASPIRATION FOR PRIMARY CELL CULTURE AND HISTOPATHOLOGICAL EVALUATION - TECHNICAL NOTE

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OBJECTIVE: Ultrasonic aspiration has been widely adopted in the resection of tumors of the central nervous system. In the past, the tumor tissue fragments obtained have been discarded. To evaluate these fragments as possible sources of material for histopathological study and tissue culture, we compared the microscopic features and viability in tissue culture of CUSA tissue fragments and biopsies obtained by conventional methods. METHODS: Brain tumor tissue obtained by ultrasonic aspiration (CUSA EXcelTM, Integra Radionics, Inc.) into a simple suction trap during resection was processed for primary cell cultures. Samples were cleared by centrifugation, washed with DMEM (Invitrogen, Darmstadt, Germany) and digested with trypsin 30 minutes at 37°C for at least one time until no fragments could be explored. Cells were seeded in DMEM as monolayer cultures supplemented with 10% heat-inactivated fetal calf serum, 100U/ml penicillin and 100 μg/ml streptomycin, and 2mM L-glutamine (all Invitrogen, Darmstadt, Germany). Further, cells were cultured in T75 tissue culture flasks (Greiner BioOne, Frickenhausen, Germany) at 37°C and 5% CO2 in a humidified atmosphere. Cell viability was measured by WST-1 Test and immunohistological evaluation was performed in the Institute of Neuropathology. RESULTS: Eight cases (one meningioma, two metastasis, and 5 gliomas) are presented to demonstrate that these tissue fragments retain good preservation of histological detail and tissue culture viability. CONCLUSION: Brain tumor tissue available from a simple suction trap during resection with the CUSA ExcelTM (Integra Radionics, Inc.) is consistently greater than that obtained by standard biopsy methods. Utilization of this material may facilitate pathological interpretation by providing a more representative sample of tumor histology as well as providing an adequate and sterile source of material for tissue culture studies.

P.007. IDENTIFICATION OF STEM-LIKE GLIOBLASTOMA CELLS WITH ABERRANT SELF-RENEWAL USING A COLLAGEN-BASED SELF-RENEWAL ASSAY

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Stem-like tumor cells endowed with enhanced self-renewal capacity are believed to influence tumor growth in malignant gliomas. So far a variety of surrogate markers has been proposed to enrich these cells emphasizing the need of devising new isolation methods based on common functional and phenotypic criteria. In this study we used the neural colony-forming cell assay (NCFCA) to screen for clonogenic cell subpopulations in glioblastoma. In a large panel of cell lines (n = 23) we identified several cell lines enriched for cells with enhanced self renewal capacity and tumor-forming capacity. Employing isolation and re-plating techniques, we were able to identify individual cells with the unique ability to reinitiate growth of secondary cell clones. Through label retention experiments we could further show, that these cells invariably reestablished a cellular hierarchy in terms of self-renewal capacity through a series of asymmetric cell divisions. However, the ratio of symmetric to asymmetric cell divisions seemed to be pathologically increased. Finally, we were able to establish a link between the increased self-renewal in these cell lines *in vitro* and a poor overall survival of the corresponding patients. Altogether, the NCFCA was found to be a valuable, marker-independent assay to study cells with aberrant self-renewal capacity and tumor-formation capacity in glioblastoma.

P.008. EXPRESSION AND FUNCTION OF PRECOCIOUS DISSOCIATION OF SISTERS 5A (PDS5A) IN HUMAN MALIGNANT GLIOMAS

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OBJECTIVE: At genetic level Glioblastoma multiforme (GBM) are characterized by a high degree of chromosomal instability and aneuploidy. Normally, the mitotic checkpoint ensures intact spindle mircrotubulibinding to sister chromatids in the G2/M phase of the cell cycle. Defects in this checkpoint cause chromosomal instability and may be tumorigenic. Additional proteins regulating sister chromatid cohesion may also be involved in maintaining the fidelity of chromosome segregation. Precocious dissociation of sisters 5A (Pds5A) is a nuclear protein expressed from S phase through mitosis. It plays a role in the establishment, maintenance and dissolution of sister chromatid cohesion. Mutation of its orthologs in lower organisms results in chromosome missegregation, aneuploidy, and DNA repair defects. Such defects may either induce apoptosis or be cancerogenic and altered expression levels have been observed in diverse malignancies. Recently, we published first data concerning this protein in malignant gliomas. However, its specific function, its expression especially under hypoxic conditions - as they are found in GBM - and its correlation with tumor development and patient's outcome have not been analysed so far. METHODS: We analysed expression of Pds5A in a panel of 15 astrocytoma WHO grade 2 (LGA) and 15 GBM by semiquantitative and quantitative RT-PCR and Western-blotting. Pds5A protein expression was examined in addition by immunohistochemistry in matched samples of 24 LGA and 14 GBM (10 primary and 4 secondary GBM). Tumor grade, recurrence of disease and patients survival was correlated with Pds5A expression. The effect of siRNA provoked Pds5A downregulation on mitotic checkpoint function, proliferation, viability, apoptosis and sister chromatid resolution was then analysed in U251 cells and the effect of hypoxia (5% and 1% O_2, respectively) was included in these examinations. RESULTS: Pds5A was significantly overexpressed at both the mRNA and protein level in human gliomas, correlating positively with the WHO grading. Pds5A knock-down did not influence mitotic checkpoint function or proliferation and survival of GBM cells, but did affect sister chromatid cohesion. 15% chromosome spreads prepared from Pds5A depleted cells displayed unresolved sister chromatid arms compared to 7% in the control siRNA treated cells. CONCLUSION: Although the mechanism by which Pds5A functions in GBM cells remains unclear, its

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overexpression in high grade gliomas and its requirement for sister chromatid separation imply that it could participate in occurence of aneuploidy and thereby that it could play a pivotal role during development and progression of astrocytic tumors.

P.009. EXPRESSION OF A DUAL SPECIFICITY PROTEASE FIBROBLAST ACTIVATION PROTEIN IN HUMAN HIGH-GRADE GLIOMAS

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High-grade gliomas are highly vascularised tumors with extensive infiltration of the surrounding brain parenchyma, and the inability to target the dispersed glioma cells is one of the major reasons for the failure of current treatment strategies. Fibroblast activation protein (EC 3.4.21; FAP) is a dual specificity serine dipeptidyl peptidase and gelatinase that is strongly associated with the development, progression and outcome of human carcinomas and represents a potential therapeutic target. The gelatinolytic activity of FAP in stromal as well as tumor cells is presumed to collaborate with other proteases on the modification and degradation of extracellular matrix and thus tumor invasion and metastasis, but other mechanisms were also suggested including cleavage of biologically active peptides and nonezymatic functions. However, the role of FAP in human malignancies is complex as it may also act as a tumor suppressor. Relatively little is known about the expression and function of FAP in human astrocytic tumors. In our study, we detected increased FAP mRNA expression in approximately 50% of high-grade gliomas compared to controls (pharmacoresistant epilepsy patients). However, higher expression of FAP could be detected in the large majority of high-grade gliomas on the protein level. Interestingly, FAP was localized not only in the GFAP+ parenchyma cells but strong staining of the GFAP- cells surrounding blood vessels was also observed. FAP was expressed albeit variably in primary cell cultures derived from high-grade gliomas, glioma cell lines and tumors xenotransplanted in immunodeficient mice. In glioma cells, FAP was localized on the plasma membrane, but to a great extent also intracellularly. To determine the influence of FAP on glioma cells and the possible underlying molecular mechanisms, we established transfectants inducibly expressing enzymatically active and mutant, enzymatically inactive human FAP. Somewhat surprisingly, transgenic expression of FAP in U373 glioma cells led to reduced migration, invasion in collagen gels, reduced adhesion to collagen I, but not fibronectin, and changed cellular morphology. These effects were not observed in cells expressing a mutant, enzymatically inactive form of FAP. In summary, FAP is expressed in human high-grade gliomas in GFAP+ glioma cells and may influence their adhesive and invasive properties probably by means of its intrinsic enzymatic activity. Further, its localization in perivascular GFAP- cells implies its role in the excessive neoangiogenesis in glioblastoma. Further studies are ongoing to assess the association of FAP expression with clinicopathological data and patient survival, as well as to determine its role in neoangiogenesis and glioma invasion in vivo. This work was supported by grants IGA 12237-5/2011 and PRVOUK-P27/LF1/1.

P.010. MITOTIC CHECKPOINT FUNCTION AND EXPRESSION OF ITS KEY REGULATORY PROTEINS UNDER NORMOXIC AND HYPOXIC CONDITIONS IN HUMAN MALIGNANT GLIOMAS

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OBJECTIVE: Chromosomal instability, aneuploidy and hypoxia are hallmarks of Glioblastoma multiforme. The mitotic spindle checkpoint controls fidelity of spindle attachment to chromatids and thereby of chromosome segregation. Defects in this checkpoint may lead to aneuploidy and tumorigenesis. Hypoxia disturbs chromosome segregation and normally activates the mitotic checkpoint. Therefore, a weakened mitotic checkpoint in conjunction with hypoxic conditions may accelerate chromosomal instability and participate in increasing malignancy of GBM. METHODS: We examined checkpoint function in GBM cell lines U87, U251 and U343 under normoxic and hypoxic (5% and 1% O2, respectively) conditions by FACS analysis after Nocodazole (0.075 μM, 1 μM and 3 μM) induced spindle damage. Next, we investigated alterations in mRNA and protein expression of the key checkpoint proteins MAD1, MAD2, MAD3, BUB1, BUBR1, BUB3 and MPS1 in the above mentioned cells and in human tissue samples of astrocytoma WHO °II and Glioblastoma by semi-quantitative RT-PCR and Western Blotting. Finally, real time measurements (xCELLigence, Roche) were used to monitor how altered MAD2 expression levels influence checkpoint function, proliferation rates and survival of GBM cells. RESULTS: In U87, U251 and U343 cells the mitotic checkpoint generally was functional. However, under normoxic conditions high Nocodazole concentrations (> 1 μM) caused a complete G2/M arrest, while low Nocodazole concentrations of 0.075 μM allowed cells to slip through the checkpoint causing a higher rate of aneuploidy and apoptosis. Cell culture under severe hypoxia (1% O2) revealed a weakened mitotic checkpoint, since cells continued to proliferate even if spindle damage was induced by 1 μM Nocodazole. Protein expression analysis showed upregulation of Bub1 concomitantly with increasing WHO grading. MPS1 was overexpressed by tumor tissue. MAD2 expression was very diverse in glioma tissue samples from different patients. Such alterations in expression of key regulators of the mitotic checkpoint perturb its function. The real-time experiments demonstrated that MAD2 expressing cells arrested after Nocodazole treatment. Knock-down cells continued to proliferate, and MAD2 overexpression led to reduced proliferation rates. CONCLUSION: Mitotic checkpoint function is weakened in GBM cells, probably due to alterations in checkpoint protein expression levels. Such variations may cause an imbalance in the checkpoint signalling network and therefore may have implications for efficacy of GBM standard therapy. Special attention has to be directed to hypoxia, since it escalates the effect of checkpoint malfunction to chromosomal missegregation. Normalization of checkpoint protein expression levels could stabilize the chromosomal content, activate the mitotic checkpoint under radiation and chemotherapy and slow down tumor growth rates.

P.011. SHP1 EXPRESSION IS EPIGENETICALLY REGULATED AND INFLUENCES THE SENSITIVITY TO CHEMOTHERAPEUTIC AGENTS IN GLIOBLASTOMA CELLS

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INTRODUCTION: Glioblastoma is characterized by chemoresistance. One factor than can contribute to chemoresistance is aberrant DNA methylation of specific genes relevant for drug response, e.g. tumor suppressor genes. AIM: The aim of this study was to investigate whether the tumor suppressor gene SHP1 is epigenetically regulated and if its overexpression affects the sensitivity to chemotherapeutic drugs with different mechanisms of action in glioblastoma cell lines. METHODS: Differences in methylation levels in the SHP1 promoter and SHP1 protein expressions between untreated cells and cells treated with the demethylating agent decitabine were analyzed with bisulfite Pyrosequencing and Western blotting. Differences in drug sensitivity to a panel of chemotherapeutic drugs with different mechanisms of action between SHP1 overexpressing clones and control clones were analyzed with the fluorometric microculture cytotoxicity assay. RESULTS: We demonstrated that SHP1 promoter methylation was correlated to SHP1 expression and that the expression was increased upon demethylation. Overexpression of SHP1 resulted in lower ($p < 0.05$) sensitivity to the proteasome inhibitor bortezomib and the alkylating agents cisplatin and melphalan. CONCLUSION: SHP1 expression may be epigenetically regulated and its overexpression influences the sensitivity to chemotherapeutic drugs in glioblastoma derived cells.

P.012. OMICS ANALYSIS OF THE ANTI-GLIOMA EFFECT OF CILENGITIDE

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BACKGROUND: Integrins are expressed in tumor cells and tumor endothelial cells, and they play important roles in angiogenesis and invasion in glioma. Cilengitide (EMD121974), an inhibitor of integrins, demonstrated preclinical efficacy against malignant glioma. It is speculated that Cilengitide, which

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inhibits the adhesive function of integrins, can inhibit tumor growth, invasion, and angiogenesis. However, the effects of Cilengitide on these processes have not been sufficiently examined. In this study, we investigated the anti-glioma effect of cilengitide using DNA microarray analysis. METHODS: U87ΔEGFR cells (human malignant glioma cell line) were used for this experiment. The cells were harvested for 16 h of Cilengitide treatment, and mRNA was extracted. Gene expression analysis, gene ontology analysis, and pathway analysis were performed using a DNA microarray (CodeLinkTM Human Whole Genome Bioarray). RESULTS: The expression of 264 genes was changed with Cilengitide treatment. The expression of 214 genes was up-regulated by 4-fold and the expression of 50 genes was down-regulated by 0.25-fold compared to the controls. In gene ontology analysis, genes that were associated with "activation of pro-apoptotic gene products" were over-represented, and genes that were associated with "negative regulation of neuron apoptosis" were over-represented. In pathway analysis, "apoptotic cleavage of cellular proteins" and "TNF receptor signaling pathway" were over-represented. Apoptotic-associated genes such as caspase 8 were up-regulated. CONCLUSION: Omics analysis revealed more detailed mechanism of the anti-glioma effect of Cilengitide. Genes associated with apoptosis were over-represented following Cilengitide treatment.

P.013. IS THE RASSF1A/HIPPO PATHWAY AT THE BEGINNING OF GLIOMA?

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INTRODUCTION: The tumor suppressor gene RASSF1 encodes a protein, RASSF1A, leading to several cellular processes especially apoptosis and cell migration by its heterodimerization with RasSF5. This initiates a cascade of kinases phosphorylation activating MTS1/2 then LATS1/2. RASSF1 is frequently inactivated in various cancers and brain tumors. However the methylation status of its partners has remained largely uninvestigated. Previously we reported the frequent alteration of all these proteins by hypermethylation in primary glioblastoma (pGB) suggesting their involvement in gliomagenesis. Here, we adress such hypothezis by analyzing the promotor methylation of RASSF1A and partners in various grades of gliomas. MATERIALS AND METHODS: Methylation specific PCR (MS-PCR) was performed from DNA extracted from paraffin blocks of 137 gliomas (36 grade II, 50 grade III and 51 grade IV) for each promoter studied (RASSF1/5, LAST1/2, MST1/2). 78/ 86 grade II and III gliomas were oligodendroglial or mixed gliomas. RESULTS: We confirmed the high methylation frequency of RASSF1A promoter in pGB (64.7%) which was no exclusive with the methylation of other Hippo members pathway (LATS1: 9.8%, LATS2: 13.7% MST1: 5.9%, MST2: 2%). No hypermethylation was found for RASSF5 in pGB. Frequency of RASSF1A promoter methylation (~78%) or RASSF5, MST1/2 promoter (~11% each) were similar in grade II and III whereas LATS1/2 methylation, respectively at 8.3 and 36.1% in grade II gliomas, reached respectively 18 and 50% in grade III gliomas. Surprisingly, LATS2 methylation was twice more present in tumors with oligodendroglial component (45 vs. 25%) whatever the grade. Conclusion. This study represents the first report of the hypermethylation profile of RASSF genes and partners in gliomas of various grades. These data show a high prevalence of the RASSF1A/Hippo Pathway in gliomas including low grade gliomas which supports the hypothesis that such alterations might initiate gliomagenesis. This study also warrants further investigation of the frequent epigenetic inactivation of LATS2 in oligodendroglial tumors.

EPIDEMIOLOGY

P.014. EGFR EXPRESSION AND GLIOBLASTOMA OUTCOME

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INTRODUCTION: Glioblastoma, the most common and aggressive subtype of glioma is associated with poor prognosis and few prognostic factors are known. The epidermal growth factor receptor (EGFR) has been associated to booth glioma risk and prognosis, playing a key role in glioma progression. The receptor is amplified in approximately 50 % of glioma cases and glioblastoma with EGFR amplification often have a constitutively active receptor due to a mutation in the EGFR receptor gene (EGFRvIII). EGFR over expression has been associated with poor prognosis in low grade glioma and anaplastic astrocytoma. MATERIAL AND METHODS: This study is based on 124 glioma cases from Denmark originally collected between 2000 and 2004 as part of the Interphone study. On all cases clinical data on surgery, chemotherapy, radiotherapy and follow-up was collected. The EGFR expression was measured using immunohistochemistry, and the results was divided in to four groups, negative, low, moderate and strong. Hazard ratios (HR) for increasing EGFR expression was calculated using the Cox regression model. The negative cases where set as the categorical variable. The HR were adjusted for age, gender, gross total resection or not, radiotherapy and chemotherapy. RESULTS AND DISCUSSION: We found a trend towards shorter survival with increasing EGFR expression, low expression HR 1.14 95% CI (0.62-2.11) $p = 0.68$, moderate expression 1.84 95% CI (0.95-3.57) $p = 0.07$ and strong expression HR 2.58 95% CI (1.52-4.36), $p = 0.0004$. This was not significant when controlling for age, sex, surgery, radio- and chemotherapy. No significant difference was seen when analysing glioblastoma cases separately. This could be due to small sample sizes as there were only 66 glioblastoma cases and data on follow-up and treatment was missing in several cases.

P.015. RECENT TRENDS IN OCCURRENCE OF PRIMARY BRAIN TUMORS IN KUMAMOTO PREFECTURE, JAPAN

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BACKGROUND: The increased use of neuro-imaging techniques and various environmental factors, have led to a change in the incidence and proportions of types of intracranial tumors. To date, no accurate population-based epidemiological study of intracranial tumors in Japan has been reported. We evaluated recent trends in the occurrence of primary intracranial tumors among residents of Kumamoto Prefecture, Japan. METHODS AND RESULTS: We surveyed 6,251 new cases of primary. intracranial tumors diagnosed in Kumamoto Prefecture between 1989 and 2010. The overall age-adjusted incidence rate was 14.09 (males:11.59, females:16.38) per 100,000 population per year. The most common tumors were meningiomas (37.4%), followed by gliomas (19.1%), adenomas (17.6%), schwannomas (9.8%), and brain lymphomas (3.7%). There was an increase in the incidence of asymptomatic meningiomas in the elderly. Between 1997 and 2010, the number of asymptomatic meningiomas diagnosed per year was higher than of symptomatic meningiomas. The number of gliomas also increased. Between 1989 and 2010, the age-adjusted incidence rate of glioma was 2.79(males: 3.10, females; 2.41) per 100,000 per year, in the 5-year period from 2006 and 2010, the glioma incidence rate was 3.13(males 3.77, females: 2.59) per 100,000 per year. The number of brain lymphomas also increased; the incidence rate between 2006 and 2010 was 0.75(males:0.77, females:0.74). Our survey of 240 patients younger than 15 years who were diagnosed with primary brain tumors showed that the incidence rate of medulloblastoma and germ cell tumor was 3.7 (boys: 2.4, girls: 5.0) and 4.6(boys:7.1, girls: 2.2) per million children, respectively. DISCUSSION: Although we adjusted the population in Kumamoto Prefecture based on the Japanese population, we observed that the rate of several types of intracranial tumors increased. The incidence of glioma continues to be lower in Kumamoto Prefecture than Western countries, while the incidence of brain lymphoma in Kumamoto Prefecture is approaching that recorded in Western countries. The incidence of germ cell tumors in Kumamoto Prefecture was twice as high as in Western countries while the incidence of medulloblastoma was less than half of that in Western countries. CONCLUSION: Our findings suggest that differences between Kumamoto and Western countries in the incidence of glioma, medulloblastoma, and germ cell tumors is attributable toracial differences.

P.016. PATTERNS OF CARE AND SURVIVAL OF GLIOBLASTOMA PATIENTS: A COMPARATIVE STUDY BETWEEN 2004 AND 2008

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BACKGROUND: The treatment of glioblastomas (GBMs) has significantly changed since 2005. However, to what extent this change has improved the overall survival (OS) of the patients treated outside clinical trials remains to be fully determined. The objective of the present study was to compare the patterns of care and the OS of all of the GBM patients diagnosed in 2004 and in 2008 at the Pierre Wertheimer Neurological and Neurosurgical Hospital in Lyon, France. METHODS: All of the patients with a diagnosis of GBM in 2004 and in 2008 were included using the pathological data files. The medical files of all patients were reviewed. RESULTS: One hundred and five patients were diagnosed with a GBM in 2004 and one hundred and thirty in 2008. Younger patients (aged < 70 years) diagnosed in 2008 received more frequently a temozolomide radiochemotherapy as initial treatment and bevacizumab at recurrence than those diagnosed in 2004 (69% vs 26% p < 10-4 and 41% vs 3% p < 10-4). Elderly patients (aged ≥ 70 years) diagnosed in 2008 received more frequently an oncological treatment (radiotherapy and /or chemotherapy) than those diagnosed in 2004 (67% vs 38%, p = 0.006). The patients diagnosed in 2008 had a longer OS than those diagnosed in 2004 (10.5 months vs 5.3 months, p = 0.001). This was true for both younger and elderly patients (15.3 months vs 8.9 months, p = 0.02 and 6.4 months vs 3.2 months, p = 0.0002). CONCLUSION: In our center the change of patterns of care of GBMs between 2004 and 2008 has been associated with a significant improvement of the OS in both younger and elderly patients.

P.017. TUMOR-ASSOCIATED EPILEPSY IN PATIENTS SUBMITTED TO SURGICAL RESECTION AT THE INSTITUTO NEUROLOGICO DE COLOMBIA IN A TEN-YEAR PERIOD: A RETROSPECTIVE ANALYSIS

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BACKGROUND: Worldwide, about 65 million people are estimated to have epilepsy. Epilepsy is common in patients with brain tumors, and the frequency of tumoral epilepsy is 30% or more, depending on tumor type. OBJECTIVE: To describe the main characteristics of patients with brain tumors and epilepsy who underwent surgical resection at the Instituto Neurologico de Colombia. METHODS: A retrospective analysis was undertaken during a 10-year period (2001-2011). We collected patient's clinical, electroencephalographic, neuroimaging, and histological features. Surgical outcome was also considered. RESULTS: A total of fifty patients with intractable epilepsy and intracranial neoplasm were identified, of whom 35 were excluded; the remaining fifteen comprised the population of the study. Corresponding demographic information included 10 women (66.7%) and 5 men (33.3%), with a mean age of seizure onset of 17 years (SD 14.07). Tumor diagnosis using neuroimaging techniques was made at a mean age of 25 years (SD 13.4) and in half of the population such findings were made 4.5 years following seizure onset (IQR: 1-12). The mean presurgical seizure frequency was 16 per month (SD 11.9); 93.3% of patients presented with partial seizures and in 86.7% auras were reported. Electroencephalographic abnormalities included focal activity in 77% of the population. Among primary CNS neoplasm, tumor location was: temporal (60%); frontal (33.3%) and parietal (6.7%). Tumor resection was performed at a mean age of 26 years (SD 13.5). Based on histopathological findings, the most common tumor types encountered included: astrocytoma (33.3%), ganglioglioma (26.7%), dysembryoplastic neuroepithelial tumor (DNET) (13.3%), gangliocytoma (6.7%), glioblastoma (6.7%), hamartoma (6.7%) y choroid plexus papilloma (6.7%). DNET was reported as the most epileptogenic neoplasm, according to seizure frecuency. Sixty-nine percent of patients had significant postoperative seizure improvement (Engel's classes I and II) and one patient died due to respiratory failure in the early postoperative period. CONCLUSIONS: Epileptic seizures are common in patients with brain tumours, and epileptogenesis is probably multifactorial. These findings highlight significant seizure improvement in tumor-associated epilepsy patients following surgical resection. KEYWORDS: Epilepsy; Brain tumor; Seizures

QUALITY OF LIFE

P.018. SHORT MINDFULNESS-BASED COGNITIVE THERAPY (MBCT) TO DEPRESSION, FATIGUE, AND DISABILITY IN BREAST CANCER PATIENTS: A PRELIMINARY RANDOMIZED CONTROL STUDY

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PURPOSE: MBCT group appears to be an efficacious intervention for use among people affected by cancer who also experience symptoms of depression and anxiety. This study is to assess the efficacy after MBCT treatment of depression and fatigue symptoms in breast cancer patients at least 2 weeks after radio or chemotherapy. Patients were randomized into MBCT group and treatment-as-usual group (TAU group) to see the therapeutic effect of psychotherapy and changes of patients' level of disability related to fatigue, anxiety and depression. The Institutional Review Board of Kaohsiung Medical University approved the study. METHOD: This is a prospective study. The Beck Depression Inventory (BDI), Beck Anxiety Scale(BAI), validated Quick Assess of Fatigue Scale-6 items-Chinese version (QAFS-C) and Sheehan Disability Scale(SDS) were applied to 21 breast cancer patients (MBCT group, N = 10; control group, N = 11)at two times: at the start of MBCT (T1), and the endpoint of MBCT(T2). MBCT was administered by well-trained psychologists through 4-6 individual therapy sessions. RESULTS: There were significant reductions within MBCT group in depression (P = 0.01), anxiety (P = 0.00), fatigue symptoms (P = 0.04) and level of disability (P = 0.00) following the intervention. While TAU showed non-significant changes during observation period. Results showed participants' scores on measures of depression and anxiety decreased and related reduction to levels disability after short term treatment with the residual mood and fatigue symptoms 2weeks after chemo and radiotherapy,. CONCLUSIONS: Depression and fatigue symptoms increased during radio or chemo-therapy treatment and residual symptoms remained even after the end of therapy, while disability levels worsened in social, family and career domains. At the end of treatment, nurses need to advise patients with residual mood and fatigue symptoms to psychiatric consultation, offering interventions to decrease these symptoms and improve functional disability.

P.019. THE TWO-WEEK WAIT RULE FOR SUSPECTED CNS/BRAIN TUMOURS IN THE UK: A DECADE ANALYSIS OF REFERRAL PATTERNS, GUIDELINE COMPLIANCE AND DIAGNOSTIC EFFICACY

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INTRODUCTION: The two-week wait (2WW) referral guideline for suspected central nervous system (CNS)/brain tumours was implemented in the UK more than a decade ago to facilitate early cancer diagnosis with the overall aim of improving CNS/brain tumour survival rates. This study aimed to provide a decade analysis of referral patterns, compliance and diagnostic efficacy of the guideline. METHOD: All patients referred via the 2WW guideline for suspected CNS/brain tumour to the Department of Neurosurgery (Newcastle) from 1st January 2002 to 31st December 2011 were retrospectively identified from the local cancer registry. Data from referral letters, case notes, radiographic images and final outcomes were recorded. Trends in waiting time, time to diagnosis, compliance and detection rates, and effectiveness of the guideline in identifying CNS/brain tumours were analysed. RESULTS: Of 85 2WW referrals, 41.2% were non-compliant and 21.2% identified CNS/brain tumours. The detection rate was higher in referrals that complied with the guideline compared to those that did not (32.0% vs 5.2%, P< 0.05). The guideline had a high sensitivity of 88.8% (63.9-98.1%, 95% CI) and low specificity of 49.2% (40.0%-61.6%). Most of CNS/brain tumour diagnoses were made independent of the 2WW pathway (N = 1093, 98.4%). Over the last decade, there were no significant changes in trends in waiting time, time to diagnosis and compliance and detection rates. CONCLUSION: The efficacy of the 2WW guideline for CNS/brain tumours implemented by the UK Department of Health is questionable. An urgent revision of the criteria and guideline education training for general practitioners are recommended.

P.020. THE CAREGIVERS' PERSPECTIVE ON THE END-OF-LIFE PHASE OF GLIOBLASTOMA PATIENTS

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OBJECTIVE: Glioblastoma multiforme (GBM) still harbors a fatal prognosis. The involvement of the psyche and neurocognition poses

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unique challenges for care provision by relatives. We lack data about the caregivers' perspective on the end-of-life (EOL) phase of GBM patients to improve counseling and supporting them and their proxies. METHODS: In this retrospective study we investigated the experiences of 52 caregivers of deceased GBM patients treated in two hospitals in Vienna, Austria. We used a questionnaire specifically developed by the University of Amsterdam for exploration of the EOL phase in patients with malign brain cancer. RESULTS: The caregivers (17m/34f) responded the questionnaire in median three years after the patients' death. 88% of them were the patients' partners. The most common caregiver-reported symptoms of patients with GBM in the EOL phase were fatigue (87%), reduced consciousness (81%) and aphasia (77%). 22% of patients were bedbound during their last three months increasing to 80% in the last week of life. 29% of the caregivers reported that they felt incompletely prepared for their tasks and about the illness of their loved ones. 46% of the patients died in hospitals and 40% at home, whereas 79% of the patients had expressed the wish for dying at home. The leading symptoms of caregivers were sadness (90%), fear (69%) and burnout (60%) and did not differ significantly between caregivers of patients, who died at home and caregivers of patients, who died in hospitals. CONCLUSION: The caregiver reported that their quality of life (QOL) was only slightly better than the QOL they attributed to the patients, emphasizing the urgent need for support and training dedicated to caregivers.

P.021. REHABILITATION TREATMENT IN PATIENTS WITH PRIMARY BRAIN TUMORS

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BACKGROUND: The actual problem of neuro-oncology is development and application of optimal methods of rehabilitation treatment (RT) in patients with primary brain tumors. The main criterion of treatment efficiency in patients with brain tumors is quality of life. AIM AND METHODS: The tactics of rehabilitation treatment was developed based on the complex assessment of results in 830 patients with primary brain tumors. The data of clinical-neurological examination and results of MRI, CT, fMRT and SPECT were used for selection of the differentiated methods of RT. Postoperative treatment course includes pharmacotherapy, electro-miostimulation, laser-therapy, medical gymnastic and massage. Postoperative treatment courses were determined by the level of neurological deficit, localization of a tumor, its extension into eloquent areas and malignancy grade. Comparative analysis of neurological status in pre- and postoperative period was performed using the Karnofsky Performance Scale (KPS). RESULTS: The developed methods of rehabilitation treatment in patients with primary brain tumors allowed optimizing of the treatment in postoperative period. During the rehabilitation treatment after surgical removal of primary brain the percent of patients with KPS score ≥ 70 has increased from 43,9% to 85,6% ($p \leq 0,05$). CONCLUSION: The use of developed tactics of rehabilitation treatment in patients with primary brain tumors provides the ability for social rehabilitation and promotes the higher levels of quality of life.

P.022. PATIENT INFORMATION.

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For the wellbeing of the patient and the family it is essential to receive clear information, as well to have regular exchange with the specialist and the multidisciplinary team. When a diagnosis of a brain tumour is made, after a series of tests, the patient will often be in a state of shock. In order to understand and feel in control of the situation many patients search information on the Internet. However the enormous variety of data aimed at different audiences is likely to perturb them. An information booklet has been written by 5 psychologists to satisfy this tangible need. These authors work for many years in different neurosurgery departments in Belgium and are specialized in the support of these points. This booklet covers the most frequently asked questions raised during the patient consultation and contains:

- Realistic and scientific information comprehensive to the patient and family members.
- Encouragement to raise questions and discuss issues with doctors and their medical team.
- Information, tips and useful addresses in guide book form.

The booklet will be distributed without charge to patients and families who express interest.

P.023. COGNITIVE REHABILITATION AND QUALITY OF LIFE: WHICH IS THE RELATIONSHIP?

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INTRODUCTION: The definition of quality of life (QoL) in cancer patients refers to a multidimensional concept that encompasses the physical, psychological, emotional and social components associated with the illness and its treatment. Cognitive impairment, one of the most common among neurological deficits in neuro-oncological patients, may have a significant impact on patients'daily lives, reducing QoL, hampering patients' attemps to resume their normal work and social activities. The aim of the study was to evaluate the impact of an intervention of cognitive rehabilitation on QoL of neuro-oncological patients. MATERIALS AND METHODS: Patients with evidence of cognitive deficits at the basal neuropsychological evaluation underwent a cognitive training consisting in 1-hour-weekly individual computer-aided sessions, for 10 weeks. Inclusion criteria for the cognitive training were: 1) mild to-moderate cognitive deficits (MMSE ≥ 18); 2) life expectancy ≥ 6 months; 3) KPS ≥ 70; 4) age ≥ 18 years. All patients were re-evaluated at the end of the training. QoL was investigated by means of QLQ-C30-EORTC completed by the patients before and after the training. Subjective QoL perception was measured in all patients also with a visual-analogical scale. RESULTS: 19 patients (11M/8 F, mean age 51 $\pm$ 13.9 years, 7 glioblastoma, 7 high grade glioma, 4 low grade gliomas, 1 ependymoma) underwent cognitive training. Statistical analysis showed a significant improvement ($p < 0.05$) at the post-training evaluation. All patients reported a subjective enhancement in cognitive functioning and QoL; however no significant improvement in QoL was detected by QLQ-C30-EORTC. DISCUSSION: Despite an improvement in cognitive efficiency and a subjectively reported enhancement in QoL, patients'QoL measured by means of one of the most widely used test, does not show improvements. We believe this discrepancy can be due to the measure adopted, mainly focused on external and physical aspects to assess QoL, that may not capture other aspects, equally important, such as cognitive functions. Investigations in QoL have important clinical implications; outcome measures for neuro-oncological patients need to assess, beyond just survival and physical aspects, the many facets of QoL.

P.024. NEUROCOGNITIVE OUTCOMES AFTER SURGERY IN CHILDREN TREATED FOR BRAIN TUMOR

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Cognitive deficits are frequently reported in children with brain tumors (BT). Radio- and chemotherapy (RCT), age at surgery, length of rehabilitation period after surgery have been implicated in causing a variety of cognitive deficits. The aim of this study is the analyse of influence of these factors on intelligence and executive functions (planning and spatial working memory) in children with BT. Subjects: Three groups of children participated in research: 1) children with BT treated with RCT ($N = 14$, aged 11-17, $M = 14.0 \pm 1.49$); 2) treatment free children with BT ($N = 13$, aged 11-17, $M = 14.8 \pm 1.8$); 3) control group of typically developing healthy children ($N = 18$, aged 11-17, $M = 13.4 \pm 1.83$). METHODS: K-ABC-II (Kaufman Assessment Battery for Children, 2nd Ed.; Kaufman & Kaufman, 2004); CANTAB (Cambridge Neuropsychological Test Automated Battery; Cambridge Cognition), selected subtests: SWM (spatial working memory), SOC (stockings of Cambridge - planning). RESULTS: Analysis of covariance, controlling for age, indicated that both groups of children with BT scored significantly lower in overall intelligence. These data show that the brain tumor or/and neurosurgery have negative impact on intelligence. Moreover, we found the progressive decline in intellectual abilities

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over a rehabilitation period in both groups with BT. Children with BT treated with RCT demonstrate poor performance for planning task. No group differences were found in spatial working memory. DISCUSSION: Many researches describe lower IQ of children with various traumatic brain injuries. In early studies were found, that children who have severe brain injury might be at risk manifesting what is known as neurocognitive stall. This neurocognitive stall is a halting or slowing in later stages of cognition, social and motor development beyond a year after brain injury. Differences between planning and spatial working memory may be associated with difference neural substrates of these functions.

P.025. POST-OPERATIVE LANGUAGE DEFICIT AFTER GLIOMA RESECTION IN THE FRONTAL LOBE

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Glioma resection in or nearby the medial frontal lobe may result in immediate post-operative motor and/or speech deficits (known as the SMA syndrome). Mostly, recovery occurs spontaneously within a few weeks or months. No extensive case studies describing language functions after glioma resection in the frontal lobe are available in the LGG literature. We describe a patient (KO, 39 y.) with post-operative language problems as a consequence of a left-hemispheric glioma resection in the frontomedial region within the SMA area. KO developed a strong reduction of the spontaneous speech during awake craniotomy. Naming and repetition remained intact. The follow-up of this patient was conducted at 2 weeks, 7 weeks and 3 months post-operatively with a neurolinguistic protocol: spontaneous speech, sentence completion measured with reaction time, repetition, naming and comprehension. Control groups: A. Normals: Spontaneous speech ($n = 21$, mean age 38 y.) Sentence completion ($n = 18$, mean age 33 y.) B. Glioma patients ($n = 27$, mean age 37 y.) pre- and 3 months post-operation. Pre- and post-operation, KO's performance on naming, repetition and comprehension tasks was intact. His pre-operative spontaneous speech however was slightly deviant (>2sd normals). Language performance was characterized by incomplete sentences, self-corrections and repetitions. Post-operatively, the strong reduction of the spontaneous speech during the awake operation was still present at 2 weeks after surgery. Compared with pre-operation, KO used more repetitions (>2sd normals and patients) and shorter utterances. At 7 weeks post-operation there was only a slight improvement, but at 3 months post-operation KO spontaneous speech was better than pre-operatively apart from repetitions. The sentence completion task was only administered post-operatively because of his per-operative speech reduction. Compared to healthy controls KO deviated (>2sd) 2 weeks post-operation on 75% of the sentence completion task (with no response on 1 subpart), 7 weeks post-operation on 75% (without no responses), and 3 months post-operation on 50%. Progress was made predominantly in the production of new sentences with a word or sentence cue. A spontaneous speech analysis and the sentence completion tests appeared to be valuable diagnostic instruments, because these tools were able to capture the patient's problems in daily conversation. We suggest that language problems after glioma resection in the medial frontal lobe are relatively transient. This information is valuable for both patients and clinicians. Patients can be informed pre-operatively about their expected prognosis. Spontaneous recovery of language deficits decreases the risk for resections of gliomas in the frontomedial region.

P.026. SHOULD WE PERFORM SURGERY FOR GLIOMAS? - PATIENT' POINT OF VIEW

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BACKGROUND: Gliomas are the second most frequent type of cerebral tumors after the metastatic ones. Treatment for types III and IV according to WHO classification includes surgery, chemo and radio therapy. The influence of surgery and the extent to which it should be performed has been a subject of controversy for a long time. Although surgery has been proven to prolong life, its influence over health related quality of life (HRQOL) has never been fully documented. Because HRQOL is a very important aspect in appreciating the long term benefits of a treatment, our purpose was to determine whether surgery had a positive or negative influence from the patient's perspective. MATERIAL AND METHODS: The Quality of life questionnaire C30 (QLQ-C30) and all related material was kindly provided to us by the EORTC. QLQ-C30 was applied to patients scheduled for surgery in the Cluj County Emergency Hospital Neurosurgical Department, because of a high suspicion of malignant gliomas according to MRI results, between April 2011 and February 2012. The questionnaire was then applied a second time one month after surgery. Inclusion criteria were the patient's agreement to participate in the study and a fully intact mental status before and after surgery. 119 patients were initially included, out of which only 58 responded to the second questionnaire. RESULTS: Response rate to the second questionnaire was higher among females, patients coming from an urban environment and high education level. On the functional scales, surgery had a significant negative influence ($p = 0.04$) over social QOL and emotional QOL ($p = 0.03$). Surgery didn't exert a significant influence over role and cognitive scales ($p > 0.05$), while it had a positive influence on physical scale ($p = 0.04$). On the symptoms scales, patients showed mild improvement after surgery with p values between 0.05 and 0.08, except financial difficulties where the influence of surgery was highly negative $p = 0.01$. The greatest positive influence of surgery was over fatigue and nausea and vomiting ($p = 0.05$). CONCLUSIONS: In our study, surgery did not improve short-term health global status. Surgery may have a positive role on the disease symptoms, while it has a negative influence over emotional and social quality of life. Financial situation is severely affected by the medical treatment.

P.027. PRESERVED QUALITY OF LIFE FOR OLDER PATIENTS WITH GLIOBLASTOMA TREATED WITH REDUCED DOSE OF RADIOTHERAPY AND TEMOZOLOMIDE

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PURPOSE: To evaluate the safety, efficacy, and possibility of preserving the quality of life using short- course radiotherapy RT with concomitant and adjuvant temozolomide TMZ in patients 60 years or older with glioblastoma multiforme GBM. PATIENTS AND METHODS: Thirty patients ≥ 60 years old with newly diagnosed GBM having a Karnofsky performance status KPS of ≥60 were treated with RT 46 Gy in 23 fractions over 5 weeks concomitantly with daily TMZ 75mg/m^2 followed by TMZ 175mg/m^2 for 5 days every 4 weeks till progression. We compared the results to a historical cohort of 30 patients with similar characteristics who were treated with the conventional RT 60 Gy in 30 fractions over 6 weeks with same TMZ dose. The overall survival OS was the primary endpoint, while the progression free survival PFS, response (size of tumor, extent of edema, and the progress in the involutional changes), pre and post treatment corticosteroids dose, toxicity, and the change in KPS were secondary endpoints. RESULTS: Sixty patients were evaluable, 22 females and 38 males with median age of 66 years with a median KPS of 70 in both groups. There was no significant difference in the median OS between the 2 groups (11.75 and 12.25 months), and in the median PFS (6 and 6.5 months). The patients who received short- course RT had similar responses to the conventional group with partial response in 12 vs. 14, stable disease in 11 vs. 10, and progressive disease in 7 vs.6 patients which were non-significant. There were significant improvements in the post treatment KPS, edema, and the progression of the involutional changes as indicated by the follow up MRI in favor of the short- course RT. The post radiotherapy corticosteroid dose was increased in 7 patients (23.3%) in the current group compared to 14 patients (46.7%) in conventional group. Side effects were mild in form of Grade 3 or 4 thrombocytopenia and/or neutropenia in 6 patients of the current group (20%) with no neurotoxicity reported, which was better, yet not statistically significant, than the conventional group. CONCLUSION: Treating elderly patients with GBM by a short-course of RT plus concomitant and adjuvant TZM is safe, effective. Patients can achieve comparable OS and PFS compared to the conventional dose of RT with preserved or even improved quality of life.

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IMMUNOLOGY AND IMMUNOTHERAPY

P.028*. CLINICAL APPLICATION OF CHAPERONE HSP70 IN THE TREATMENT OF MALIGNANT BRAIN TUMORS

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INTRODUCTION: Molecular chaperons, particularly Hsp70, were shown to efficiently stimulate anti-cancer immune response. We previously reported that intratumoral application of Hsp70 in model of intracranial glioma in rodents can enhance innate and adaptive immune response. As next step in pilot study for the first time local intratumoral delivery of rhHsp70 was investigated for feasibility, safety, side effects and possible systemic anti-tumor immune responses in patients with brain tumors. Material and methods. Patients with newly diagnosed tumors without any previous treatment were enrolled in pilot study ($n = 12$). Study was conducted according to the resolution of the local ethical committee of the Russian neurosurgical institute named after prof. A.L. Polenov and patient's written consent. Intraoperationally after tumor resection silicone catheter was implanted in tumor cavity. Following operation a course of five intratumoral injections of rhHsp70 through catheter (500 μg of rhHsp70 in saline solution per single injection was infused on 1, 3, 5, 7 and 9 day after an operation; totally 2,5 mg of protein per course) were performed. During Hsp70 infusions patients received no other treatment except corticosteroid therapy. Before Hsp70 administration and after the last injection specific immune responses were evaluated in delayed hypersensitivity test (DTH). Furthermore peripheral blood was monitored for possible changes in lymphocyte subpopulations, cytokine levels, and cytolytic activity of NK-cells. Results and discussions. Intratumoral injections of Hsp70 were well tolerated in patients. One patient had objective complete clinical response and one patient partial response documented by radiological findings. In three patients we observed positive DTH-test. In peripheral blood we observed a shift from cytokines provided by Th2-helpers (IL-4, IL-6) towards cytokines of Th1-mediated response (TNF-α, INF-γ). This data corresponded to increase of overall CD3+ T-cell population (including CD4+ T-helpers, CD8+ T-killers, and activated CD3 + HLA DR+), concomitant decrease in B-lymphocytes. Levels of Treg-cells (CD4 + CD25 + FoxP3-) were also reduced, as well as serum quantity, spontaneous and induced production of IL-10. However, though there was a slight increase in NK-cells amount in peripheral blood, their cytolitic activity did not alter. CONCLUSIONS: This pilot study for the first time demonstrated feasibility and safety of intratumoral delivery of recombinant Hsp70 in cancer patients. Based on our preclinical and clinical data we proposed the hypothesis of new mechanism of immunomodulatory anti-tumor activity of Hsp70. Our results suggest that purified Hsp70 can induce specific effective anti-tumor immune response and warrants further investigation in randomized clinical trials.

P.029*. ONCOLYTIC ADENOVIRUS THERAPY OF MALIGNANT GLIOMA IN IMMUNE COMPETENT MICE INDUCES ANTI-VIRAL AND ANTI-TUMOR IMMUNE RESPONSES

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The oncolytic adenovirus Delta24-RGD has demonstrated highly effective anti-tumor efficacy in various intracranial (IC) xenograft models for glioblastoma. Species specificity of human adenovirus has restricted preclinical studies to immunocompromised animals. As a result, the role of the immune system has not been delineated and may have consequences for the efficacy of adenovirus therapy. Therefore, we set up a syngeneic immune-competent IC model with murine glioma GL261 cells that are semi-permissive to human adenovirus replication and investigated both the innate and adaptive immune response to Delta24-RGD treatment. C57BL/6 mice were injected stereotactically with GL261 cells and treated five days later with Delta24-RGD or PBS. At early and late timepoints post-treatment, brain, blood and spleens were collected. Splenocytes were exposed to Delta24-RGD or GL261 cells and assessed for IFNγ production ex vivo. Brains were used for protein lysates and sections. The lysates were assessed for several cytokines and chemokines. The tissue sections were immunohistochemically stained for various immune cells and the adenoviral protein hexon. Serum samples were tested for the presence of neutralizing antibodies. Hexon protein was present at 6, 12, 96 hr and 14 days post virus injection. A rapid influx of F4/80+ macrophages was detected within 24 hrs and enhanced numbers of CD8+ T cells were present at 14 days in treated mice when compared to control mice. MIP-1α and IP-10 showed an up-regulated expression at early time points, potentially responsible for the recruitment of monocytes and activated T cells, respectively. Several of the acute phase cytokines (IL-1β, IL-6) and IFNγ were induced at 6 and 12 hrs. However, expression of IL-2, IL-4, IL-10, IL-12, cytokines related to Th1 or Th2-type cytokine responses, was not altered at any of the timepoints tested. Splenocytes from treated animals exposed to either Delta24-RGD of GL261 tumor cells, but not control stimulations, produced increased levels of IFNγ. Finally, high levels of neutralizing antibodies were detected in the sera of mice starting 96 hours post-treatment. In conclusion, the immunocompetent GL261 murine glioma model provided a first set of data on the role of the innate and adaptive immune response to oncolytic adenovirus treatment in the brain. We demonstrate that splenocytes, most likely CD3+ T cells from Delta24-RGD-treated mice recognize both virus as well as tumor antigens, information that is valuable in further design of oncolytic viral therapies.

P.030*. DICLOFENAC INHIBITS LACTATE FORMATION AND EFFICIENTLY COUNTERACTS LOCAL IMMUNE SUPPRESSION IN A MURINE GLIOMA MODEL

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Lactate formation in highly proliferative tumors such as malignant gliomas is associated with poor survival and contributes to the suppression of local immunity. In this study, we report that diclofenac, but not celecoxib or acetylsalicylic acid inhibits lactate production in murine GL261 glioma cells by downregulating the expression of lactate dehydrogenase A (LDH-A). Lactate reduction was accompanied by a dose-dependent inhibition of cell proliferation and a cell cycle arrest at the G2/M checkpoint. *In vivo*, Diclofenac treatment of glioma-bearing mice reduced intratumoral lactate levels and resulted in a significant delay of tumor growth. *Ex vivo* analysis of tumor-infiltrating leucocytes revealed that Diclofenac markedly diminishes the number of $CD4^+FoxP3^+$ regulatory T cells (Treg) and impairs the upregulation of the Treg activation marker CD25. Moreover, we observed that tumor-infiltrating $CD11c^+$ dendritic cells regain their capacity to produce IL-12 upon Toll-like receptor stimulation with R848. However, a single intratumoral injection of R848 did not result in an additional survival advantage of diclofenac-treated mice *in vivo*. Further experiments showed that the presence of diclofenac during T cell activation compromises INF-γ production and T cell proliferation indicating that immunotherapeutic approaches have to be carefully timed when combined with diclofenac. In summary, this study indicates that diclofenac is an attractive substance to target lactate formation and to counteract local immune suppression in malignant gliomas.

P.031. TREATMENT OF TUMOUR CELL WITH 5-AZA-2-DEOXYCYTIDINE (DAC) FOR IMMUNE TUMOUR THERAPY OF GLIOMA IN FISCHER 344 RATS

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Fisher 344 rats implanted with either N29 or N32 glioma tumours were. immunized with either IFN-γ gene-transfected syngeneic tumour

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cells. or IFN-γ transfected syngeneic cells treated with 10 μM 5--aza-2-deoxycytidine (DAC). Separate groups of rats were also treated in combination with Pulsed Electric Fields (PEF) or Radiation therapy. Tumours (N29) were inoculated subcutaneously on both thighs of. female Fiscer-344 syngeneic rats. For immunization the animals were given intra-peritoneal injections of irradiated, IFNγ transfected N29 tumour cells or DAC treated IFNγ transfected cells. In the combined treatment the left tumour was treated once with 16 exponential pulses with an electric field strength of 1400 V/cm, and 1.0 ms duration (time constant). No anticancer drugs were given at any time. The following day and then once weekly for three weeks, the animals were given intra-peritoneal injections of irradiated, IFNγ transfected N29 tumour cells or DAC treated IFNγ transfected cells. The treatment results were evaluated by daily measuring the size of. tumour on both sides of the animals. Treatment with solely PEF in 32 animals resulted in a growth rate decrease of 20 ± 6 % on the PEF exposed tumour. The effect at the non targeted tumour was negligible (0 ± 4 %). Treatment with IFN-γ secreting tumour cells resulted in a significant decrease of tumour growth rate on the right tumour of 20± 2 % ($p < 0.05$) and no significant effect (3 ± 0.3%) was observed on the left tumour. Immunization with DAC treated IFNγ secreting cells in 12 animals showed no significant decreased growth rate, on neither the left nor the right tumours. By combining PEF + IFNγ no significant decrease in growth rate was achieved. But in the combination of PEF and IFNγ secreting cells grown in DAC medium the tumour growth rate decreased by about 50 % at the PEF treated tumour and there was a decrease of about 20% in tumour growth at the non-PEF treated tumour which is about the same as for PEF treatment alone. Immune therapy of rats with intracranial implanted N32 tumours by immunization with IFN-γ secreting syngeneic cells treated with DAC resulted in a slight (3%) but not significant increase in survival time. With just a single RT fraction of 15 Gy, however, there was a significant increase of 32% in the length of survival time of the rats with N32 tumours ($p < 0.02$) and when combined with immunotherapy with IFNγ transfected N32 cells the increase was about 40%. Radiation therapy with a single fraction of 15 Gy combined with immunization with IFN-γ secreting syngeneic cells treated with DAC resulted in significant ($p < 0.01$) 34% increased length of survival time for the N32 tumours although there were no complete remissions. Thus the DAC treatment of the tumour cells seems to have no benefits.

P.032*. CD317 SCFV-*PSEUDOMONAS* EXOTOXIN A IMMUNOCONJUGATE FOR THE TARGETED THERAPY OF GLIOBLASTOMA

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Glioblastoma is the most common primary malignant brain tumor. Despite multimodal therapy the prognosis remains poor with a median overall survival not exceeding 5 months in population-based studies or 15 months in selected patient groups. CD317, also known as HM1.24, is a type II transmembrane protein, which is expressed on terminally differentiated human B cells and overexpressed on malignant plasma cells. It is constitutively endocytosed from the cell surface to the trans-golgi-network and inhibits retroviral infection by preventing the diffusion of virus particles after budding from infected cells. However, its role in cancerogenesis remains unclear. Interestingly, CD317 is also overexpressed on the mRNA level *in vivo* in some solid tumor types, including glioblastoma. Moreover, CD317 expression increases with the tumor grade of astrocytomas. Here we report that CD317 is expressed heterogeneously in human glioma initiating and long-term glioma cell lines on mRNA and protein levels *in vitro*. The immunotoxin HM1.24-ETA' is a fusion protein of a HM1.24 specific single-chain Fv (scFv) fragment combined with a truncated version of *Pseudomonas* exotoxin A lacking the receptor binding domain. HM1.24-ETA' induces apoptosis in CD317-positive glioblastoma cells in a concentration-dependent manner. Interestingly, CD317 protein levels at the cell surface increase significantly when glioma cells are treated with interferon-β, resulting in increased acute cytotoxicity when these cells are co-treated with interferon-β and HM1.24-ETA'. In summary, CD317 is an interesting novel cell surface antigen on glioblastomas that can be targeted by HM1.24-ETA' immunotoxin therapy. The combination with interferon-β may enhance glioblastoma cytotoxicity. The poor prognosis of this highly lethal brain tumor type requires innovative treatments. HM1.24-ETA' may have the potential to provide a novel approach of immunotherapy for glioblastoma patients.

P.033. TOXICOLOGICAL PROFILE OF DECORIN, A NOVEL IMMUNOTHERAPEUTIC AGENT FOR THE TREATMENT OF GLIOBLASTOMA MULTIFORME

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OBJECTIVES: Current treatments for Glioblastoma (GBM) are inadequate and immunotherapeutics may provide better outcomes for patients. Human recombinant Decorin is a glycoprotein that modulates inflammation & GBM growth by inhibiting Transforming Growth Factor, Vascular Endothelial Growth Factor and Epidermal Growth Factor Receptor. As Decorin is found in human tissue rich in fibrillar collagen (e.g. skin, heart, bone lung & liver) it is a potentially safe drug to be trialled in humans. DESIGN: Rats received intercerebral injection of 5mg/ml Decorin and were sacrificed at 30min, 3 & 24 hrs. Analysis of the rat's ability to walk, grasp and eat was assessed and macroscopic evaluation of various tissues was performed. Blood, urine and CSF samples were taken and analysed by ELISA for presence of Decorin. The immune response to injections of Decorin was investigated using immunohistochemistry to identify markers of inflammation in brain. METHODS: Anaesthetised Sprague Dawley rats were injected with 5 μl Decorin or PBS control directly into the brain using a stereotactic frame at co-ordinates of 0.2mm posterior to bregma, 3mm lateral and 4mm deep. Rats were monitored for behavioural changes (ability to walk grasp & eat). At 30min ($n = 6$), 3 hours ($n = 6$) and 24 hours ($n = 6$) rats were sacrificed and macroscopic evaluation of brain, lung, heart, liver, spleen, intestine and kidney was performed. Blood, urine and CSF samples were taken prior to rats being perfusion-fixed. Microscopic evaluation of the immune response was performed using IHC to identify cells positive for Decorin and to assess the inflammatory reaction using antibodies to OX42 and ED1 to identify microglia and macrophages. RESULTS: There was no inflammatory reaction or cavity formation in brain. No end-organ damage was visible in brain, heart, lungs, kidney and intestines. Behavioural assessments were all normal in response to Decorin injection into brain. Preliminary results shows intracranial injection of Decorin dampens the microglial response compared to controls. At 30 mins, low levels of decorin were detected (with ELISA) in CSF and serum but none was detected at 3hrs and 24hrs after injection. CONCLUSIONS: Decorin showed no dose limiting toxicity, whilst maintaining its immunomodulatory effects in brain. These findings show a safe pharmacokinetic and toxicological profile of Decorin that is now being made to GCP grade. CSF samples will be analysed using Luminex technologies to measure inflammatory cytokines after injection of Decorin into brain.

P.034. TUMOR DEBULKING AND CD56+ NK CELL RESPONSES ARE ASSOCIATED TO PROLONGED SURVIVAL IN RELAPSING GLIOBLASTOMAS TREATED BY TUMOR-LOADED DENDRITIC CELLS

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Relapsing glioblastoma (GBM) are highly aggressive tumors allowing 6-9 months survival. Here we evaluated possible clinical benefits of immunotherapy of relapsing GBM using mature DC. Fifteen patients with relapsing GBM and life expectancy of at least three months were considered in this study. After apheresis, CD14+ monocytes were isolated to high purity by immunomagnetic separation. In final preparations, 61.4% ± 16.8% DC showed positivity for CD83, a marker of maturation. Immune responses were assessed by flow cytometry and real time PCR on peripheral blood lymphocytes (PBL). Median overall survival was 7.6 months (95% CI 6.6-11.1). Patients were divided in two groups according to tumor volume at the time of first vaccination; group A, large tumors (≥10cc; $n = 7$) and group B, small tumors (< 10 cc; $n = 8$). Patients of group B survived significantly longer than others (17 months vs 6.8 months; $p = 0.009$ at Kaplan-Meir analysis). Patients from group A and B, respectively, were analysed for CD8+ T cells and CD56+ NK cells in peripheral blood at different times of treatment. NK cells increased after immunization in group B but not in group A patients. RT-PCR and serum analyses on PBL from group B showed up-regulation of E4BP4, the NK cell transcription factor, in correlation to up-regulation of IFN-γ and IL-12. The results suggest that tumor-loaded, mature DC may increase survival of relapsing GBM after effective tumor debulking and emphasize the role of CD56+ NK cells in this therapeutic setting.

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P.035*. CLINICAL STUDY PHASE II WITH DENDRITIC CELL VACCINATION AND TUMOUR LYSATE AS ADD-ON THERAPY IN HIGH GRADE GLIOMA

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AIM: To improve treatment of high-grade glioma (HGG) with immune therapy based on vaccination with autologous dendritic cells (DC) loaded with tumour-derived lysate (DCm-HGG-L). BACKGROUND: Immune therapy of CNS tumours is an emerging modality that potentially can enhance the current multimodal treatment approaches being used, because the prognosis of these patients remains poor. Therefore, as therapy being both tumour-specific and well tolerated, the intra-cutaneous vaccination by DCm-HGG-L in Sweden, a technique which has been developed by van Gool et al in Leuven, Belgium, was a good candidate. METHODS: Adult patients underwent leukaferesis after radical surgery. The DC were extracted by CD14+ enrichement with the CliniMacs platform. Blood samples for immunologic stimulation analysis (CD4, CD8) were collected prior to therapy and before each intradermal vaccination. RESULTS: Since December 2009, DCm-HGG-L has been produced at the Karolinska University Hospital Solna for HGG patients, according to a strict protocol required by the Medical Product Agency. Five patients have been treated, 4 with glioblastoma, one with recurrent supratentorial PNET. Age 20-40 yr, KPS 80-100. All underwent radical surgery followed by concomittant radiochemotherapy. Median PFS $<$ 6 mo (3-18 m) for 4/5 patients. OS: 2 patients died between 3-6 months after treatment, the 3 other are alive, 2 with recurrence. The CD4 and CD8 blasts increased and remained at high level after the 3 rd vaccine. CONCLUSION: The immunological therapy for High Grade Glioma is today available in Sweden. The treatment is safe. Further evaluation is under way to implement this strategy, especially in the adult population.

IN VITRO / IN VIVO MODELS

P.036. VASCULAR ENDOTHELIAL GROWTH FACTOR-MEDIATED PLATELET-DERIVED GROWTH FACTOR RECEPTOR ACTIVATION IN GLIOBLASTOMA

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BACKGROUND: Glioblastomas (GBM) are highly vascularised tumours with an active and persistent angiogenesis, essential for their progression. Glioma cells produce factors such as vascular endothelial growth factor (VEGF-A or VEGF), a key mediator of the angiogenic process. Anti-angiogenic therapies normally target VEGF or its receptors VEGFR1 and 2. The antiVEGF antibody Bevacizumab® has improved the outcome of GBM patients, nevertheless predictive molecular markers are lacking. Elucidation of tumour dependent predictors of response in a clinically relevant laboratory model may help to identify those patients more likely to benefit from antiangiogenics. MATERIAL AND METHODS: U87MG cell line and four primary cultures from fresh GBM (P14, P19, P33 and P35) were established to test the effects of VEGF and other angiogenic factors (EGF, PDGF-BB and FGF-2) on receptor tyrosine kinase phosphorylation and signal transduction by western blot. Cell proliferation was determined by thymidine incorporation assay and VEGFR-2 and VEGF expression was measured by RT-PCR. A human phospho-RTK assay was used in order to determine which receptors were being stimulated by VEGF and PDGF-BB. RESULTS: two of the primary cultures (P33 and P14) and U87MG cells were stimulated by VEGF and resulted in increased ERKs phosphorylation. In addition, VEGF also stimulated cell proliferation in U87MG cell line. All these results were obtained in the absence of expression of VEGF receptors. In addition U87MG expressed high levels of VEGF mRNA and only P33 cells produced small amounts of VEGF. Incubation of P33 cells with VEGF and PDGF-BB identified PDGFRβ as the main receptor activated in response to VEGF in our primary cultures using a phosphoRTK array. Moreover, PDGFR tyrosine kinase inhibitors (imatinib and sunitinib) prevented the VEGF mediated signalling transduction events. CONCLUSION: our results suggest that VEGF activates glioma cells through PDGF receptorβ. Further studies testing PDGFRβ activation as a predictor of response to antiVEGF or antiPDGFR treatment in GBM are warranted.

P.037. CELL CULTURE SPECTROSCOPY (CECUSY) - A MULTIVARIATE APPROACH TO NMR SPECTROSCOPY OF CULTURED BRAIN TUMOR-INITIATING CELLS

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NMR spectroscopy (NMRS) of cultured brain tumor-initiating cells (BTIC) is a unique approach to quantitatively and non-invasively investigate metabolic aberrations with respect to non-initiating tumor cells and to physiological neural cell types. High-resolution *in vitro* studies of cellular extracts, on the one hand, and, on the other hand, NMRS of living cells proved their informative value in revealing significant differences between different neural cell types, between physiological cells and tumor cells, and between different stem cell types, e.g. regarding amino acid composition, choline metabolism, glycolysis, and lipid droplet formation. We propose a new approach to cellular NMR spectroscopy that combines the explanatory power of five cell culture-adapted NMRS methods, namely (1) NMRS of cell culture supernatants/conditioned media which yield information on metabolic flux from the cell culture medium into the cells and *vice versa*; (2) NMRS of cellular lysates that provide an insight into intracellular water-soluble metabolites, e.g. by means of a methanol-water extraction methodology; (3) NMRS of lipid extracts in order to draw conclusions on cell membrane and lipid droplet compositions; (4) NMRS of intracellular protein preparations that yield information on total protein contents as well as on their relative amino acid compositions, e.g. via denaturation and solubilization procedures based on urea and guanidine or via complete protein hydrolysis; and (5) NMRS of living cells that are perfused with adjustably oxygenated and temperature/pH-controlled medium during long-term measurements. For all five cell culture NMRS methods, we provide protocols that describe optimum culturing, harvesting and sample preparation techniques, adapted NMRS acquisition methods, e.g. pulse sequences and acquisition parameters, optimized quantification strategies, e.g. least squares approaches using model spectra from metabolite spiking experiments, and databases. Aiming at a complete NMR spectroscopic insight into what discriminates the small tumor subpopulation of BTIC from the majority of non-initiating tumor cells, this new multivariate approach, tentatively named CEll CUlture SpectroscopY (CECUSY), could provide both further targets for future treatment strategies as well as novel surrogate biomarkers for non-invasive monitoring of tumorigenesis and treatment efficacy.

P.039. CURCUMIN AND AZD6244 SYNERGIZE TO PROMOTE ANOIKIS IN APOPTOSIS-RESISTANT GLIOMA CELLS VIA DOWNREGULATION OF STAT3 AND CYCLIN D1 AND UPREGULATION OF P21 AND BIM

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BACKGROUND: Evasion of anoikis or detachment-induced apoptosis plays an important role in cancer cell survival during dissemination and establishment of secondary tumors. Many signaling pathways like JNK, PI3K/AKT, FAK, and ERK are known regulators of anoikis. In addition, Bcl-2 family members are vital for cell survival after detachment. The involvement of the Stat3 pathway in anoikis of glioma cells has not been investigated. MATERIALS AND METHODS: Tu-9648 glioma cells were derived from a spontaneous murine glioma. Stat3 and MAPK/ERK signaling was inhibited with the non-toxic, natural compound curcumin and the MEK-selective, and ATP-uncompetitive compound AZD6244. Inhibition of active pY-Stat3 and pERK1/2 was analyzed by Western blotting. Effects on cell growth, cell migration and cell invasion were measured by MTT viability, wound-healing and Boyden chamber assays. Effects on gene expression were quantified by TaqMan® PCR. Cells kept on poly-HEMA-coated dishes served as in vitro model of anoikis. RESULTS: Curcumin treatment sensitized the apoptosis-resistant glioma cells to anoikis and caspase-independent cell death. Prolonged curcumin treatment

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led to tremendous vacuolisation and eventually to detachment of the glioma cells. Curcumin-induced anoikis was paralleled by strong up-regulation of the pro-apoptotic BH3 family protein Bim EL. Coincident with Bim EL upregulation active pERK1/2 diminished in the detached cells, thus preventing proteosomal degradation via phosphorylation of serine 69 in the Bim EL protein. Combinatorial treatment of glioma cells with curcumin and AZD6244 further increased the upregulation of p21 and Bim EL as well as the downregulation of Cyclin D1 transcripts as measured by quantitative RT-PCR. CONCLUSION: These results show that concurrent MEK inhibition can reinforce the cytocidal effect of curcumin against glioma. The expected therapeutic benefit of the combinatorial treatment has to be corroborated in vivo using mice with intracranially transplanted Tu-9648 glioma cells. This novel drug combination may serve as a new therapy regimen for malignant glioma.

P.040. INHIBITION OF RAT AND HUMAN GLIOMA CELL LINE PROLIFERATION AFTER ADMINISTRATION OF THE GLYCOPROTEIN, DECORIN

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OBJECTIVES: Glioblastoma multiforme (GBM) is the most aggressive primary brain tumour. Human recombinant Decorin - a glycoprotein that inhibits Transforming Growth Factor (TGFβ), Vascular Endothelial Growth Factor (VEGF) and Epidermal Growth Factor Receptor (EGFR) - may suppress GBM growth. DESIGN: Growth rates of *in vitro* GBM cell lines were determined with addition of Decorin or medium alone (control). Decorin's mechanism of action was investigated using combinations of selective inhibitors for TGFβ, VEGF and EGFR with and without Decorin. METHODS: C6, U87 and primary human (grown from patients) GBM cells were plated at a density of 200,000/ml in complete medium. Serum free medium containing Decorin was administered to cells by repeated doses of 100ug/ml/24hr +/- 40uM AG1478 (inhibiting EGFR), 100ng/ml Bevacizumab (inhibiting VEGF)or 10uM Smad2/3 (inhibiting TGFβ). Control groups contained serum free medium +/- protein kinase inhibitor only. Daily cell counts were analysed with T-Tests. RESULTS: From 200,000 baseline, C6 cell counts increased to 700,000 after 3 days incubation. Single dose Decorin reduced growth: 100mg/ml grew only 420,000 cells ($p < 0.005$). After 5 days of repeated daily Decorin dosing, cell counts in C6 cells were 505,000 (controls = 1,280,000, $p < 0.001$) and in primary cells were 300,000 (controls = 667,500, $p < 0.001$). Moreover, Decorin *reduced* cell numbers in U87 cells to 180,000 (controls = 550,000, $p < 0.001$). Inhibition of EGFR and VEGF in C6 or U87 cells did not markedly reduce cell counts compared to controls alone but the addition of Decorin to these inhibitors yielded significant decreases in cell numbers. Preliminary data suggests the TGFβ inhibitor alone reduced cell numbers by approximately 50% compared to controls in both cell lines. This suggests that the addition of Decorin to TGFβ did not reduce cell counts as much as its additional effects to the EGFR and VEGF inhibitors. CONCLUSIONS: Decorin abrogates growth of glioma cell lines and primary GBM cells. Adding Decorin enhances the effect of exisitng EGFR and VEGF inhibitors in reducing the rate of glioma cell proliferation. Our preliminary studies show its actions may primarily be through the TGFβ pathway. Combinatorial inhibition studies are ongoing to fully elucidate Decorin's mechanism of action. Future studies will investigate the effects of Decorin *in vivo* using a rodent model of GBM.

P.041. POTENTIAL IMAGEABLE THERAPEUTIC PROBE: GENETICALLY ENGINEERED *SALMONELLA TYPHIMURIUM* TARGETING BRAIN TUMOR MODEL

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OBJECT: Brain tumor is the most devastating and difficult-to-treat cancer with short survival. One of the main reasons is lack of effective methods for drug delivery. It has been reported that *salmonella* can target systemic tumor regions after intravenous injection into tumor-bearing mice for drug delivery. Therefore we proposed an optical bioluminescence imageable of brain tumor model, and then investigated that model whether targeting by genetically engineered *Salmonella typhimurium*. MATERIALS AND METHODS: U87 malignant glioma (U87-MG) and Lewis lung cancer cell (LLC) both stably transfected with Fluc were implanted into C57BL/6NC or BALB/cAnN nude mice by stereotaxic injection into the striatum. After brain tumor formation, *Salmonella typhimurium-ΔppGpp-Lux* was injected into tail veil. Bioluminescence signals from transfected cell or bacteria were monitored by cooled CCD camera (IVIS 100) to show the tumor location or to trace the migration of the salmonella. Immunofluorescence staining also performed in frozen section of mouse brain tumor. RESULTS: We demonstrated that optical bioluminescence detectable of brain tumor model is faithful, reproducible and consecutively detectable by cooled CCD camera (IVIS 100). Noninvasive imaging showed the *Salmonella typhimurium-ΔppGpp-Lux* exclusively localized in the brain tumor region of U87MG and LLC bearing mice. Immunofluorescence staining also demonstrated that *Salmonella typhimurium* accumulated in the brain tumor. CONCLUSION: we established a brain tumor model that can be tracked by optical bioluminescence imaging to indirectly evaluate tumor status. Our data indicate that salmonella *Salmonella typhimurium* can target brain tumor, and provide us an imaginable therapeutic probe for brain tumor.

P.042. NOVEL ANIMAL GLIOMA MODELS THAT SEPARATELY EXHIBIT TWO DIFFERENT INVASIVE AND ANGIOGENIC PHENOTYPES OF HUMAN MALIGNANT GLIOMAS

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OBJECTIVE: Invasive behaviors of malignant gliomas are fundamental traits and major reasons for treatment failure. Delineation of invasive growth is important in establishing treatment for gliomas and experimental neuro-oncology could benefit from invasive glioma model. In this study, we have established two new cell line-based animal models of invasive glioma. METHODS: Two cell lines, J3T-1 and J3T-2, were derived from the same parental canine glioma cell line, J3T. These cells were inoculated to establish brain tumors in athymic mice and rats. Pathological samples of these animal gliomas were examined to analyze invasive patterns in relation to angiogenesis, and were compared with human glioblastoma samples. Moreover, molecular profiles of these cell lines were also shown. RESULTS: Histologically, J3T-1 and J3T-2 tumors exhibited quite different invasive patterns. J3T-1 cells clustered around newly developed vessels at tumor borders, whereas J3T-2 cells showed diffuse single cell infiltration into surrounding normal parenchyma. In human malignant glioma samples, both types of invasion were observed concomitantly. Molecular profiles of these cell lines were analyzed by immunocytochemistry and QRT-PCR. VEGF, MMP-9, HIF-1, and PDGF were overexpressed in J3T-1 cells than in J3T-2 cells, whereas integrin aVb3, MMP-2, nestin, and SPARC were overexpressed in J3T-2 cells than in J3T-1 cells. CONCLUSION: The described animal models histologically recapitulated two invasive and angiogenic phenotypes, namely angiogenesis-dependent and -independent invasion, also observed in human glioblastoma. These cell lines provided a reproducible in vitro and in vivo system to analyze the mechanisms of invasion and angiogenesis in glioma progression.

P.043. THE INTEGRIN ANTAGONIST CILENGITIDE ENHANCES ANTI-TUMOR EFFECT OF VASCULOSTATIN-EXPRESSING ONCOLYTIC VIRUS

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INTRODUCTION: Oncolytic viral (OV) therapy has been considered as a promising treatment modality for malignant glioma. We investigated OV therapy-induced changes in the tumor microenvironment and found that the secretion of several proangiogenic factors can induce angiogenesis and encourage growth of residual tumor after viral clearance. The vasculostatin, the fragment of brain-specific angiogenesis inhibitor-1(BAI-1), shows anti-angiogenic activity against malignant gliomas. Previously, vasculostatin-expressing

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oncolytic HSV-1 (RAMBO; Rapid Antiangiogenesis Mediated By Oncolytic virus) has been reported to have potent antitumor effect against malignant glioma. Here we investigated the therapeutic efficacy of combination of RAMBO and cilengitide, integrin inhibitor, for malignant glioma. METHODS: Cilengitide was generously provided by Merck KgaA and the National Cancer Institute, NIH. In vitro, the scratch wound assay and the cell viability assay were conducted to assess the combined treatment with RAMBO and cilengitide by using human microvascular endothelial cells (HMVEC) and U87ΔEGFR human glioma cells, respectively. In vivo, seven days after implantation of U87ΔEGFR glioma cells into nude mouse brain, RAMBO or solvent (control) was injected stereotactically into brain tumor and treated with either cilengitide or solvent intraperitonealy 3 times a week. The survival of mice in each group was analyzed by the Kaplan-Meier method. RESULTS: In vitro, cilengitide treatment reduced the rate of wound closure of HMVEC. Especially, combining cilengitide with CM of RAMBO significantly decreased the wound closure. Combining cilengitide with RAMBO induced synergistic cytotoxicity on U87ΔEGFR glioma cells in vitro. In vivo, there was a statistically significant increase in survival of mice treated with combination therapy compared to RAMBO or cilengitide monotherapy. CONCLUSIONS: These results indicated that cilengitide enhaced new vasculostatin-expressing OV therapy for malignat glioma and provides a rationale for designing future clinical trials combining the two agents.

P.044. *IN VIVO* CHANGES OF GLIOMA CANCER STEM CELLS ACCORDING TO GENERATION

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There is increasing evidence that glioma arise from glioma cancer stem cells (gCSCs). However, there is little known regarding changes in biological characteristics of gCSCs in serial *in vivo* subtransplantation. In this study, we evaluated and compared the biological characteristics of gCSCs as it was serially subtransplanted. We hypothesized that biological characteristics of gCSCs would change through serial subtransplantion. We isolated gCSCs from human glioma specimens according to methods for culturing gliomasphere. The isolated gCSCs from glioma specimen were term generation0-glioma cancer stem cells (G0-gCSCs). Through serial *in vivo* subtransplatation, we obtained subsequent gCSCs(G1-gCSCs, G2-gCSCs). We draw a comparison between G0-gCSCs, G1-gCSCs, and G2-gCSCs by growth curve, surface markers associated with gCSCs. To evaluate *in vivo* characteristics, we implanted gCSCs from each generation into brains of nude mice and monitored mice survival. All generation were spheroid and had similar growth curves. Surface marker analysis showed that every generation had similar surface marker expression (CD133, Nestin, Podoplanin). All generation had the capacity of neural differentiation. However, there were significant differences in median survival through serial *in vivo* subtransplantation. In the immunohistochemistry, there were significant increase in cell counting stained with CD31 and TUNEL, not PCNA. In our study, serial subtransplantaion changes the biological *in vivo* characteristics while retaining *in vitro* characteristics. In addition, there was increasing of vascular proliferation and decreasing apotosis through serial *in vivo* subtransplantation. We could assume that these *in vivo* changes in biological characteristics resulted from stroma and microenviroment change through serial *in vivo* subtransplantation.

PREDICTIVE BIOMOLECULAR MARKERS

P.045*. GALECTIN-1 AS AN ONCOTARGET IN MALIGNANT GLIOMAS

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Galectin-1, a 14.5-kDa β-galactoside-binding protein, is expressed by many different cell types and displays intracellular and extracellular functions. It exerts major roles in the immune system and is involved in the progression of various cancer types, including gliomas. We have previously reported that progression of malignancy in patients bearing astrocytic tumors correlates with increased tumor levels of galectin-1 and that galectin-1 is involved in the modulation of the migration of tumor astrocytes. Galectin-1, the expression of which is stimulated by hypoxia, is also a pro-angiogenic molecule. We have shown that these pro-angiogenic effects are controlled by the ORP150 protein. Indeed, transiently decreasing galectin-1 expression in glioma cells impairs VEGF maturation (and therefore VEGF secretion from glioma cells) through marked decreases in ORP150 expression. We have then evidenced that transient decrease of galectin-1 expression in experimental models of gliomas significantly increases the therapeutic benefits contributed by the alkylating agent temozolomide, which induces sustained pro-autophagic effects followed by late apoptosis in glioma cells. In addition, in glioma cells, galectin-1 has been found to modulate p53 transcriptional activity and to decrease p53-targeted gene expression, including DDIT3/GADD153/ CHOP, DUSP5 ATF3 and GADD45A. The decrease in galectin-1 expression also impairs the expression levels of other genes implicated in chemoresistance, such as ORP150, HERP, GRP78/BiP, TRA1, BNIP3L, GADD45B and CYR61. With respect to galectin-1-mediated processes of tumor immune escape, it has been demonstrated that galectin-1 secreted by cancer cells kills activated T cells and that targeted disruption of galectin-1 gene expression results in enhanced T cell-mediated tumor rejection. In fact, galectin-1 selectively controls Th1- and Th17-mediated effector functions; it also induces the differentiation of tolerogenic dendritic cells through IL-27- and IL-10-dependent pathways. Our recent preliminary findings suggest that patients with relapsed glioblastoma are likely to have higher galectin-1 serum levels, findings which could be explained by increased damage of the blood-brain barrier or appearance of a more aggressive and more resistant tumor. In addition surgery and/or chemo-radiotherapy resulted in a significant decrease of the galectin-1 serum levels. Altogether, these findings clearly point to the fact that anti-galectin-1 approaches may weaken the defenses of gliomas against radiotherapy, chemotherapy and immunotherapy/vaccine therapy; may reinforce antiangiogenic therapies; and may weaken both the invasive capacities of these cancers towards neighboring tissues. However further studies are needed to evaluate whether galectin-1 serum levels can be used as a diagnostic or prognostic marker for glioma patients.

P.046. AQUAPORIN 1 AND 4 IN 5-ALA FLUORESCENT TUMOR TISSUE

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INTRODUCTION: Fluorescence-guided surgery with 5-aminolevulinic acid (5-ALA) enables more complete resections of contrast-enhancing malignant gliomas in adults. These glial tumors are associated with cerebral edema. Aquaporins (AQP) are a family of membrane proteins that provide a major pathway for water transport in mammals. Prior studies have suggested that AQP1 and 4 may be up-regulated in glial tumors, potentially contributing to tumor-associated edema and invasion. The objective of this study was to investigate the expression of AQP1 and 4 in 5-ALA fluorescent tumor tissue which has a high specificity for high grade malignancies. METHODS: 5-ALA fluorescent samples of different tumor tissue during surgery were analyzed for AQP1 and AQP4 positivity in combination with GFAP (only for gliomas) in selective antibody testing by fluorescent activating cell sorting (FACS). Control groups were normal brain tissue without 5-ALA fluorescence and the human glioma cell line U373. Measurements were performed immediately after resection, 4 days and 14 days after primary cell culture. Furthermore, 5-ALA staining in tumor cells was also proofed by FACS. Histopathological and clinical findings of the tumors were correlated with the experimental results. RESULTS: 18 gliomas (16 high grades, 2 low grades), 6 metastasis and 3 meningeomas, which all showed a pronounced perifocal edema in the preoperative MR imaging, were analyzed. 85% of the gliomas were AQP4 and GFAP positive, whereas the AQP4-positivity decreased after 4 days cell culture to 65% and after 14 days to only 10%. 66% of the 5-ALA fluorescent metastasis tissue samples and 33% of the 5-ALA fluorescent meningioma tissue samples were AQP4 positive. AQP1 was in none of the specimens after cell culture at any time positive, especially not in combination with GFAP. 5 glial tissue samples without histology of tumor and U373 glioma cell line as control cultures were negative for AQP1 and AQP4 testing, but positive in GFAP. OAS

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and PFS were significantly lower in samples from high grade tumors. CONCLUSION: FACS is a reliable method for detecting the fluorescence signals of porphyrins and aquaporins in primary cell cultures of tumors. Further, exposure of AQP4 in 5-ALA fluorescent high grade gliomas, metastasis and even meningeomas revealed high sensitivity. In contrast, Aquaporin 1 showed no accord to 5-ALA which is correlated to malignancy. Aquaporin 4 in combination with 5-ALA could offer a therapeutic selectively targeting treatment opportunity which needs further studies.

P.047*. MEMBRANE HSP70 EXPRESSION, A HISTOLOGICAL MARKER FOR PRIMARY GLIOBLASTOMA IS ELEVATED IN PATIENTS' SERUM SAMPLES

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OBJECTIVE: Tumor cells, in contrast to non-neoplastic cells, have the capacity to translocate cytosolic heat shock protein 70 (Hsp70) on their plasma membrane in different cancer types where it can be detected specifically by cmHsp70.1 monoclonal antibody. The biological function of membrane Hsp70 remains unclear, but it stimulates immunomodulatory response by activation of natural killer cells. For the first time, we investigated the expression of membrane Hsp70 in glioblastoma within the tumor heterogenity in cell culture and in tissue and serum samples from patients with different glioma entities. METHODS: In order to clearly define the membrane Hsp70-expressing cell type within a heterogenic tumor cell culture, we performed flow cytometric analysis on different glioma subpopulations (endothelial, mesenchymal, CD133-positive cells, primary culture) and determined membrane Hsp70 secretion by ELISA from the supernatants (each subpopulation $n = 3$). Membrane Hsp70 expression was analyzed immunohistochemically in glioma with regard to tumor grading and subcellular distribution within glioblastoma tissue ($n = 49$). Also glioblastoma (GBM) entity (primary vs. secondary) was distinguished. Furthermore, serum samples of the corresponding patients were analyzed for concentration of membrane Hsp70 ($n = 49$). RESULTS: In FACS-analysis, membrane Hsp70 is strongly expressed in primary glioblastoma cell cultures and tumor-initiating CD133-positive cells, but not in other recruited host subpopulations. Supernatant of the cells showed identical membrane Hsp70 secretion profiles of the different cell types. Immunohistochemistry showed that membrane Hsp70 is selectively expressed in primary GBM, but neither in low-grade and anaplastic gliomas nor in secondary GBM. The corresponding serum samples of the patients showed that selectively patients with primary glioblastoma had serum concentrations over 2000pg/ml. DISCUSSION: In glioblastoma, we can conclude that this marker serves as tumor-specific target which is restricted to tumor cells. This marker is uniquely expressed in primary GBM and could differentiate the de-novo-origin from secondary GBM. Surprisingly, membrane Hsp70 could also be detected at higher levels in serum of patients with primary GBM. As molecular markers carry a strong prognostic and predictive value, the biological function of membrane Hsp70 has to be further analyzed in order to tailor the treatment strategy to individual cancer patients regarding their molecular profile.

P.048. GLIOMA PROFILING WITH RAMAN SPECTROSCOPY

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INTRODUCTION: Raman spectroscopy is a molecular spectroscopic technique that can analyze tissue samples within seconds without any extraction processes or dyes. In Raman spectroscopy monochromatic laser light is applied to illuminate the sample under study. Due to interaction with the molecules in the sample the reflected light shows wavelength shifts which are subsequently detected and analyzed. As a result a wavelength spectrum is obtained with specific peaks according to the molecular composition of the sample. In these spectra DNA, RNA, proteins and lipids segregate in distinct wavelength intervals. There are different histological and molecular subtypes of glioma. These subtypes differ in their RNA and protein expression. We therefore hypothesized that using Raman spectroscopy we could discriminate glioma subtypes based on RNA profiling. MATERIAL AND METHODS: Twenty glioma samples were analyzed from two separate subtypes according to the cluster assignments as published by Gravendeel et al (Cancer Res 69(23): 9065-9072). In this report 6 clusters were defined from an unsupervised cluster analysis that showed significant differences in post-operative survival times. Two clusters were selected with large differences in median survival and RNA expression. Frozen tissue samples from these cases were processed to lysates and these were subsequently analyzed with Raman spectroscopy. The obtained Raman spectra were corrected for interference of blood and normal brain. RESULTS: Two separate clusters were identified using Raman spectroscopy and these were fully congruent with the two clusters as defined by RNA profiling. CONCLUSION: Our conclusion is that using Raman spectroscopy it is possible to identify distinct glioma subtypes as defined by RNA profiling. Since this technique can be applied at much lower costs compared to molecular analysis using micro arrays it may offer a valuable tool in laboratory settings to subtype glioma samples that show different responses in experimental therapy.

P.049. GLIOBLASTOME MULTIFORME (GBM) SENSITIVITY TO TMZ IN A 3-D *EX VIVO* INVASION ASSAY CORRELATES TO AN INCREASE IN PATIENT SURVIVAL TIME

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BACKGROUND: GBM tumour progression is dependent on the tumour's ability to invade and grow into surrounding tissue. Patient tumour responsiveness to standard of care therapeutics is difficult to predict. GBM surgical samples were assessed while exposed to a panel of clinically relevant chemotherapies including Temozolomide (TMZ) using a 3-dimensional *ex vivo* invasion and growth model. The invasion and growth of representative tumour tissue fragments are hypothesized to be reflective of clinical response to therapy. GBM patients reported in this study went on to receive TMZ post-operatively. METHODS: Surgical tissue specimens placed into a nutrient-rich 3-dimensional collagen matrix and were monitored for invasion in the presence of chemotherapies for 5 days. Each chemotherapeutic was assessed for anti-tumour responses in six tissue fragments and compared to an untreated control set of six fragments. All samples were preserved for further examination of tumour growth, invasion and viability. Patient outcomes were measured from the OR / assay date onward. RESULTS: 249 CNS patient tumours were assessed to date. Each patient's tumour displayed a unique invasion and response profile. Here we report a significant correlation between a TMZ invasion inhibition of 20% or greater to 53 GBM patient outcomes. The mean age of patient was 59.4 at the time of surgical tumour removal. Mean survival time for GBM patients' whose tumours were *not* significantly sensitive to TMZ in our invasion assay was 351.1 +/- 72 days. GBM patients' mean survival for invasion assay *positive* responders to TMZ was significantly higher ($p < 0.04$) at 586.8 +/- 104.6 days. Results will continue to be compared to patient response, time to recurrence and survival up to 2 years post-surgery/assay. CONCLUSIONS: Individual response to chemotherapy is highly variable both clinically and in our *ex vivo* assessment. Pre-screening responsiveness to chemotherapies could lead to more individualized and more effective treatment of brain tumours. We report a novel assay system which generates individual patient drug profiles, and an ability to predict a statistically significant increase in patient survival in TMZ-treated patients. Further research, including a larger formal clinical trial, is warranted.

P.050*. DETECTION OF IDH1 MUTATION IN THE PLASMA OF PATIENTS WITH GLIOMA

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OBJECTIVE: The IDH1R132H mutation is both a strong prognostic predictor and a diagnostic hallmark of gliomas and therefore has major clinical relevance. Here, we developed a new technique to detect the IDH1R132H mutation in the plasma of patients with glioma. PATIENTS AND METHODS: Small-size DNA (150 bp to 250 bp) was extracted from the plasma of 31 controls and 80 patients with glioma with known IDH1R132H status and correlated with MRI data.

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The IDH1R132H mutation was detected by a combination of COLD (co-amplification at lower denaturation temperature) and digital PCR. RESULTS: The small size DNA concentration was 1.2 ng/ml (range: 0.1-6.6) in controls vs. 1.2 ng/ml (range: 0.1-50.3) in patients with glioma ($p = NS$) and 0.9 ng/ml (0.0-3.0) in low-grade gliomas vs. 1.5 ng/ml in high-grade gliomas ($p < 0.01$). The small size DNA concentration correlated with enhancing tumor volume (1.6 ng/ml (0.4-24.9) when <10 cm3 and 14.0 ng/ml (0.6-50.3) when ≥ 10 cm3). The IDH1R132H mutation was detected in 15 out of 25 plasma DNA mixtures (60%) from patients with mutated tumors and in none of the 14 patients with a nonmutated tumor. The sensitivity increased with enhancing tumor volume (3/9 in non enhancing tumors, 6/10 for enhancing volume <10 cm3, and 6/6 for enhancing volume ≥ 10 cm3). CONCLUSION: With a specificity of 100% and a sensitivity related to the tumor volume and contrast enhancement, IDH1R132H identification has a strong diagnostic value in patients not amenable to biopsy.

P.051*. COMPARISON OF MICRORNA EXPRESSION LEVELS BETWEEN INITIAL AND RECURRENT GLIOBLASTOMA SPECIMENS

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BACKGROUND: Glioblastoma is the most common primary brain tumour and is associated with resistance to treatment and high mortality. Although new therapy regimes including chemotherapy and radiotherapy increased the overall survival rates, almost all patients experience tumour recurrence. Pathobiological mechanisms leading to glioblastoma recurrence are still mostly unclear. MicroRNAs are a recently identified class of small non protein encoding RNA molecules that are approximately 22 nucleotides in length. Tumour-specific microRNA signatures have been proposed as novel indicators for tumour proliferation, aggressiveness, differentiation and metastases development for many cancer types. However, there are only few data on the involvement of microRNAs in therapy resistance and recurrence of the glioblastomas. METHODS: We selected the following 6 microRNAs with tentative relevance for glioblastoma pathobiology by means of a comprehensive literature search: microRNA181b, microRNA181c, microRNA221, microRNA222, microRNA195 and microRNA196b. We further selected 19 primary glioblastoma cases, of whom formalin fixed and paraffin embedded tissue (FFPE) tumor tissue samples of the initial operation and a re-operation for tumor recurrence were available. All cases had received standard first line treatment consisting of postoperative combined radiochemotherapy with temozolomide. We analysed the expression of the 6 microRNAs in all 38 tumor tissue samples by RT-qPCR. Expression levels were correlated with each other and with clinical parameters. RESULTS: All microRNAs except microRNA196b showed detectable levels of expressions. Comparison of the microRNA levels between first and second resections revealed a significant increase of microRNA222 (mean: 9 fold, ranging between 0.5 to 49 fold, paired t-test, $p = 0.04$), whereas no significant change was observed for the other microRNAs. Cox regression analyses showed no significant association with the expression level of any of the analysed microRNAs with the time from first to second resection (range 5 to 339 months, median 57 months). CONCLUSION: We found a significant increase of microRNA222 levels in recurrent glioblastomas as compared to initial tumors, while expression levels of microRNA181b, microRNA181c, microRNA221 and microRNA195 remained stable. It might be interesting to further investigate the role of microRNA222 in the recurrence development of glioblastoma.

P.052. VEGFA SNP RS2010963 IS ASSOCIATED WITH RESPONSE AND THROMBO-HEMORRAGIC TOXICITY IN PATIENTS TREATED WITH BEVACIZUMAB

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BACKGROUND: VEGFA is the most important angiogenic factor in glioblastoma, and anti-VEGF therapy is a major target in glioblastoma. SNP rs2010963 in the 5'-UTR enhances VEGFA expression at both transcriptional and translational levels, and may therefore influence outcome, response to anti-VEGF therapy and toxicity. PATIENTS AND METHODS: we analysed here SNP rs2010963 impact first on the survival of 954 gliomas (grade II to IV) treated with standard therapy, and then on the response -and toxicity- to bevacizumab/irinotecan therapy in a subset of 71 patients treated for recurrent glioblastoma. RESULTS: Allelic frequencies met Hardy Weinberg equilibrium and minor allelic frequencies were not different between WHO grades. $+405\ G > C$ (rs2010963) variant was not associated with progression free survival (PFS) or overall survival (OS) neither in the whole series of 954 patients, nor in grade II (362 patients), grade III (269 patients) or grade IV glioma (323 patients). In the subset of 71 GBM patients treated with bevacizumab, $+405\ G > C$ (rs2010963) was associated with response, with CC haplotype significantly more represented in the responders group (p trend value= 0.019). The same trend was observed for PFS during bevacizumab therapy for the three haplotypes (2.87 months (GG), 4.50 months (CG), 6.63 months (CC); log rank p= 0.060). This result was confirmed by Cox regression stratified analyse (HR 0.63; p value: 0.034). OS survival did not differ significantly between the three haplotypes. Surprisingly we observed also a strong association between (rs2010963) allele C homozygosity and the occurrence of thrombo-hemorragic events during bevacizumab therapy (p value $<$ 0.0001). CONCLUSION: our data suggest that rs2010963 status has not prognostic impact in gliomas, but may predict response and thrombo-hemorragic toxicity in patients treated with bevacizumab.

NEW DRUG DELIVERY METHODS

P.053. GLUTATHIONE PEGYLATED LIPOSOMAL DOXORUBICIN (2B3-101) TARGETING THE CNS: PRECLINICAL RATIONALE AND PHASE I/IIA STUDY DESIGN FOR TREATMENT OF RECURRENT MALIGNANT GLIOMA AND BRAIN METASTASES

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The overall prognosis in patients with recurrent malignant glioma is generally poor. This is partly due to the aggressiveness of the disease but is also a consequence of the limited treatment options available. Glioma cells are not chemotherapy resistant per se, but most of these drugs have a poor blood-brain barrier (BBB) penetration at clinically feasible plasma concentrations. Although the BBB is partly disrupted in glioma, this may have only a limited impact on drug efficiency. Chemotherapy also needs to be effective in areas with diffuse glioma infiltration, where the BBB is still intact. To address this issue, glutathione PEGylated liposomal doxorubicin (2B3-101) was developed to safely enhance the delivery of this chemotherapy to the brain by targeting the glutathione transporters at the BBB. In a mouse glioma model (U87MG-luc), we have previously shown that 2B3-101 was markedly superior to conventional pegylated liposomal doxorubicin (Caelyx®) at the same dose level in inhibiting brain tumor growth and prolonging survival. Additional open-flow microperfusion studies in healthy rats receiving one intravenous dose of 2B3-101 showed that the doxorubicin brain concentrations were more than three times higher compared to brain levels obtained with Caelyx injections. Finally, no major differences were observed between 2B3-101 and Caelyx in GLP toxicity studies in rats and no cardiotoxicity or neurotoxicity was observed with any of the two compounds. The currently ongoing clinical trial with 2B3-101 has started with a dose-escalation phase ($3 + 3$ design) in patients with recurrent malignant glioma and solid tumors with brain metastases. 2B3-101 is administered as an infusion every three weeks according to the following dose schedule: 5, 10, 20, 30, 40 mg/m2 and so on, until the Maximal Tolerated Dose (MTD) has been reached. Once the MTD is established, 14 more patients with recurrent malignant glioma and 14 patients with progressive brain metastases from breast cancer will be enrolled in an expanded open label phase IIa study. The primary study objective of the dose-escalation phase is to determine the safety, tolerability and the MTD of 2B3-101. All signs of potential toxicity will be assessed, with a special focus on potential neurotoxicity and cardiotoxicity due to the

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nature of the investigational product. The secondary objectives are to assess the pharmacokinetics and preliminary anti-tumor activity of 2B3-101. The plasma concentrations of 2B3-101 are being measured during treatment cycle 1. The preliminary CNS tumor activity is assessed by MRI of the brain throughout the study, with a focus on the patients participating in the expansion phase. The first two cohorts of the dose-escalation phase have been completed without dose-limiting toxicities (DLTs). The enrollment of the third cohort is being initiated in March 2012 (dose level 20 mg/m2). ClinicalTrials.gov Identifier NCT01386580.

P.054. PROSCILLARIDIN A, A NEW DRUG FOR GLIOBLASTOMA TREATMENT?

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Gliomas are the most common primary brain tumors in adults. Among them, glioblastoma multiforme (GBM) represent the ultime grade of malignancy with poor prognosis. They are characterized by molecular and cellular heterogeneity, angiogenesis, high proliferation rate as well as a significant invasive ability which is the major cause of disease recurrence. Although, the standard therapeutic protocol called "Stupp protocol" combining surgery followed by adjuvant radiotherapy plus temozolomide has lead to an increase in median survival, however, prognostic remains dismal. In this context, we aimed to evaluate the potential usefulness of a highthroughput screening approach to determine whether novel anticancer compounds with anti-proliferative and anti-migrative activities could be identified. Surprisingly, while screening the Prestwick chemical library (1.120 molecules), three cardiac glycosides showed the most significant effects on the three GBM cell lines we analyzed: U87-MG (ATCC origin), GBM6 and GBM9 (cancer stem cells lines derived from two GBM and established at our laboratory). Among them, proscillaridin A, a cardiotonic inhibitor of the Na^+/K^+ ATPase pump, showed a significant inhibitory effect on the proliferation and migration abilities of the three GBM cell lines. We noticed a high level of cytotoxicity and the effect was dose-dependent with an IC50 of 30 nM. At low concentration (13 nM), proscillaridin A causes a disruption of cell adhesion and rapid cell death. According to these results and to other relevant studies, *in vivo* analyses were set up in *nude* mice. The subcutaneous injection of 5.10^5 U87-MG, GBM6 or GBM9 cells produces, after three weeks, solid and well individualized tumors. Ten mice were injected per cell line. As soon as tumors reached 5 mm, 5 mice per cell line were injected i.p. daily with 7 mg/kg proscillaridin A (maximum tolerated dose in animals). The tumor sizes and clinical status were recorded every two days during three weeks. At the end of the treatment, we observed, for the three cell lines injected, a significant decrease (or arrest) of tumor growth in treated mice as compared to controls. Moreover, in a small series, it has been shown that i.p. injected-proscillaridin A exhibited the same growth-arrest effect on orthotopic U87-MG tumors. Combination of histological, morphological and immunohistochemical investigations of the excised tumors reveal that proscillaridin A causes a significant decrease in cell proliferation associated with a significant increase of cell death. Our results show that cardiac glycosides and especially proscillaridin A could represent an original therapeutic alternative for the treatment of glioblastomas.

P.055. ADJUVANT CHEMOTHERAPY FOR BRAIN TUMOURS DELIVERED VIA A NOVEL INTRA-CAVITY MOULDABLE POLYMER MATRIX

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INTRODUCTION: Despite the invasive nature of high grade glioma, most relapses occur within 2cm of the surgical resection cavity. Administering chemotherapeutic agents locally into the resection cavity circumvents the blood brain barrier, potentially targeting micro-deposits of cancer cells in the brain parenchyma whilst minimizing toxic doses systemically. Here we evaluate the clinical utility, toxicity and sustained drug release capability of a novel self-assembling formulation of poly(lactic-co-glycolic acid) (PLGA)/poly(ethylene glycol) (PEG) microparticles, which potentially offers several advantages over Gliadel®. METHODS: PLGA/PEG microparticle-based matrices were pasted around an ex vivo brain pseudo-resection cavity and analyzed using MRI and CT. Matrices were subjected to a standard isocentric high dose radiotherapy regime and microparticle structure assessed. In vitro toxicity of the polymer was assessed using both tumour and endothelial cells and sustained drug release of etoposide-, methotrexate- and trichostatin A-loaded matrices was determined. To verify drug activity, tumor cells were seeded onto drug-loaded matrices and viability assessed. RESULTS: PLGA/PEG matrices can be molded around a pseudo-resection site ex vivo with good apposition to the cavity wall and with no polymer-related artifact on MRI and CT scans. The polymer withstands fractionated radiotherapy, with no disruption of microparticle structure. No toxicity was evident when tumor or endothelial cells were grown on control matrices in vitro. Trichostatin A, etoposide and methotrexate were released from the matrices over a 1-3 week period in vitro and followed near zero-order kinetics after an initial burst, with released agents retaining cytotoxic capabilities. CONCLUSIONS: The PLGA/PEG delivery system offers an innovative intra-cavity approach to administer chemotherapeutics for improved local control of brain tumors. Matrices show good apposition around a resection cavity wall and are distinguishable in clinical scans. Matrices are non-toxic in vitro suggesting good biocompatibility in vivo. Active trichostatin A, etoposide and methotrexate can be released gradually from matrices, with radiotherapy unlikely to interfere with release. Tolerability studies are currently ongoing using both subcutaneous and orthotopic xenograft mouse models, which will assess neurotoxicity from the polymer and efficacy of etoposide. Additional efforts are in progress to encapsulate drugs within microspheres in order to both minimize the initial burst phase and to permit long-term local delivery of unstable compounds such as temozolomide. The PLGA/PEG mouldable drug-delivery system will be widely applicable for childhood and adult brain tumours for which local control is an essential part of the treatment strategy.

NEUROIMAGING OF BRAIN TUMOURS

P.056. DISPLAYING TUMOR HETEROGENEITY - AN INTRA-INDIVIDUAL COMPARISON OF MRI, ^{18}F-FET AND ^{18}F-FLT PET IN HIGH GRADE GLIOMA

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OBJECTIVES: In this retrospective PET study we compared the amino acid tracer O-(2-[(18)F]fluoroethyl)-l-tyrosine (^{18}F-FET) with the nucleotide tracer 18F-3′-fluoro-3′-deoxy-l-thymidine (^{18}F-FLT) to detect additional areas of active tumor and to better define tumor borders as compared to MRI in patients with high grade glioma (HGG). METHODS: We examined 26 patients with recurrent (n = 23) and newly diagnosed (n = 3) HGG by ^{18}F-FET, ^{18}F-FLT, and MRI. Intrasubject co-registration was performed to allow direct comparison of segmented tumor volumes between all imaging modalities. In PET images, metabolically active tumors were segmented by applying a threshold to the uptake ratios. Tumor volumes on contrast-enhancing T1 (cT1) and hyperintense T2 were calculated using a semi-automatic image segmentation process. Tumor volumes and location calculated from the four modalities were compared to each other and to progression free survival (PFS) at 12 months using Mann-Whitney U test (MWU), Spearman's rank correlation and Dice's coefficient of agreement. RESULTS: Sensitivity for the detection of a HGG was lower for ^{18}F-FLT than for ^{18}F-FET (88% vs 96%). ^{18}F-FLT uptake was absent in tumors showing no or moderate contrast enhancement, missing two patients with ^{18}F-FET positive HGG (1 GBM WHO IV, 1 OA WHO III). ^{18}F-FLT volumes correlated strongly with cT1 and moderately with ^{18}F-FET volumes ($r = 0.916$ and $r = 0.655$, $p < 0.001$, respectively), while ^{18}F-FET volumes showed a moderate correlation with cT1 ($r = 0.679$, $p < 0.001$).

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^{18}F-FET uptake outside cT1 was present significantly more often compared to ^{18}F-FLT ($p < 0.001$, MWU). Taking registration and threshold errors into account, significant ^{18}F-FET volume was detected beyond the margins of cT1 and ^{18}F-FLT in 14 and 18 cases, respectively and ^{18}F-FLT uptake was detected beyond cT1 and ^{18}F-FET in one and seven cases, respectively. HGG patients with a PFS > 12 months ($n = 12$) showed a significant worse overlap of ^{18}F-FET and ^{18}F-FLT with cT1 than patients showing recurrence within the first 12 months of disease ($n = 11$, $p = 0.045$ and $p = 0.007$ respectively, Dice's coefficient of agreement, MWU). CONCLUSION: ^{18}F-FET is more sensitive than ^{18}F-FLT to detect HGG. ^{18}F-FLT shows a strong correlation with contrast enhancement on MRI and is false negative in HGG with only moderate or no contrast enhancement. Therefore, blood brain barrier breakdown seems to be a prerequisite for ^{18}F-FLT tracer uptake into the tumor. HGG patients with a tumor recurrence after 12 months of disease duration are characterized by a poor concordance of metabolic imaging with MRI, probably reflecting increasing tumor heterogeneity with longer disease duration. Consequently, metabolic PET imaging is particularly useful for re-operation or re-irradiation planning in patients with longer disease duration, favouring ^{18}F-FET-PET over ^{18}F-FLT-PET.

P.057. FLT ACCUMULATION INDICATES THE TUMOR PROLIFERATION RATHER THAN THE BLOOD-BRAIN BARRIER BREAKDOWN

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OBJECT: A PET tracer [18F] 3'-deoxy-3'-fluorothymidine (FLT) is a thymidine analog being used for the evaluation of tumor proliferation. However, there has been a controversy that FLT-PET would depict only a contrast enhancement due to the blood-brain barrier disruption but not reflect the tumor proliferation at all. Aim of this study is to clarify if FLT accumulation in glioma would not reflect the tumor proliferation but indicate the tumor enhancement on MRI. METHOD: From 2006 to 2011, patients of 36 men and 48 women, mean age 51.4 y (ranged:1 to 84 years old) were included in this study. Eighty-four astrocytic tumors (WHO grade II:19, grade III:23, and grade IV:42) identified by MRI were analyzed by DICOM software, measuring that maximum pixel value of the contrast enhanced lesion (TVmax), average pixel value of opposite normal brain (NVavg) as background level. The degree of contrast enhancement on MRI as an indicator of the blood-brain barrier breakdown was calculated by TVmax/NVavg (MRI T/N). We checked a correlation between MRI T/N, FLT accumulation (tumor/normal ratio on FLT-PET, FLT T/N) and Ki-67 labeling index (Ki-67 LI). RESULT: Mean MRI T/N, FLT T/N and Ki-67 LI was 0.55 (ranged: 0.82 to 3.68), 7.53 (ranged: 0.49 to 35.69) and 24.2(ranged: 1 to 90), respectively. Analysis using ANOVA showed both MRI T/N and Ki-67 LI correlated significantly to FLT T/N ($p = 0.0006$ and $p < 0.0001$, respectively). MRI T/N was also significantly correlated to Ki-67 LI ($p = 0.0010$). Simple linear regression analysis demonstrated FLT T/N correlated more strongly to Ki-67 LI ($R2 = 0.46$) than to MRI T/N ($R2 = 0.135$), and poor correlation between MRI T/N and Ki-67 LI ($R2 = 0.144$). Per WHO grade, MRI T/N correlated moderately to Ki-67 LI in grade II ($R2 = 0.333$) but not in grade III ($R2 = 0.082$) and grade IV ($R2 = 0.125$), while correlations between FLT T/N and Ki-67 were moderate among all grades of the tumor. (grade II: $R2 = 0.38$, grade III: $R2 = 0.468$, and grade IV: $R2 = 0.295$). CONCLUSION: In glioma, the degree of contrast enhancement eventually correlated to the degree of proliferation. Therefore, a certain contribution of the contrast enhancement on MRI to FLT accumulation should be taken into consideration. On the presupposition of such confounding, we could interpret the FLT accumulation would explain the tumor proliferation also rather than only a blood-brain barrier breakdown as indicated by contrast enhancement on MRI.

P.058. USEFULNESS OF FDG, MET AND FLT-PET STUDIES FOR THE MANAGEMENT OF HUMAN GLIOMAS

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OBJECTIVE: The use of positron imaging agents such as FDG, MET and FLT is expected to lead the way for novel applications toward efficient malignancy grading and treatment of gliomas. In this study, the usefulness of three PET scans was retrospectively reviewed by comparing their histopathological findings. METHODS: The following patients received PET scans: 27 patients with WHO grade IV (26 glioblastoma multiforme, and 1 gliosarcoma), 18 patients with WHO grade III (13 anaplastic astrocytoma, 4 anaplastic oligoastrocytoma, and 1 anaplastic oligodendroglioma) and 12 patients with WHO grade II (9 diffuse astrocytoma, 2 oligoastrocytoma, and 1 oligodendroglioma) from April 2006 to March 2012. The resulting PET scans were compared by measuring SUVs and T/N ratios. Regarding the area with a high intensity signal on the MRI (FLAIR), based on a predetermined ROI, T/N ratios of FDG, MET and FLT were used to compare the values between FDG and MET, FLT and MET, and FDG and FLT. RESULTS: There was a significant difference in the T/N ratios of FLT-PET scans between WHO grades III and IV, but similar to the MET study, there were no significant differences between the grade II gliomas and the grade III gliomas. When the accumulation of MET or FLT within the tumor and the Ki-67 index were compared, linear regression analysis revealed a significant correlation between the Ki-67 index and MET T/N ratio or FLT T/N ratio. FLT, compared to MET, demonstrated a significantly strong correlation with the proliferation ability. In glioblastoma patients, there were differences in the accumulation of each tracer within the same tumor due to the unique characteristics of each tracer, which may reflect the tissue-specific differences. This indicates that the relationship between FLT and MET is divided into three parts. We can predict that there are many oligodendroglioma components in the area with high MET but low FLT accumulation, and it is likely that the area is necrotic with low MET but high FLT accumulation. Importantly, areas with high MET and FLT accumulations were also high in Ki-67 index and were histologically highly malignant. Nine patients with tumor recurrence and three patients with radionecrosis were determined by these PET scans. In the recurrence group, the increase of the FLT T/N ratio was observed whereas in the radionecrotic group, the decrease was observed. Regarding the FDG and MET T/N ratios, various results were provided between these two groups. In low-grade glioma, it was useful to determine malignant transformation to grade III with the increased FLT and MET T/N ratios. CONCLUSIONS: PET imaging is a non-invasive modality that is useful in determining a tumor area for removal as well as improving preoperative diagnosis for gliomas, identification of tumor area for removal, determination of therapeutic effectiveness and prediction of prognosis.

P.059. 99MTC-TETROFOSMIN BRAIN SPECT IMAGING IN INTRACRANIAL LESIONS

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PURPOSE: In patients with intracranial lesions it is not uncommon CT and conventional MRI to provide non-specific information, even after contrast infusion. Imaging of intracranial space-occupying lesions by SPECT or PET provide information about the metabolic status of various brain tumors. SPECT contrary to PET has the relative advantages of lower cost, wide availability, stable radioligands with relative long half-life. In the present study we set out to evaluate 99mTc-Tetrofosmin (99mTc-TF) brain SPECT in the characterization of intracranial space occupying lesions. METHODS AND MATERIAL: We prospectively studied patients with intracranial space occupying lesions that were admitted in the neurosurgical department and underwent brain SPECT with 99mTc-TF between September 2004 and September 2011. Patients were included in the study if they had an untreated primary brain lesion suspicious of tumor on MRI and there was a histological verification of the final diagnosis. RESULTS: Radiotracer accumulation in tumors was first assessed visually. Then a semiquantitative method of image analysis was applied, by calculating the lesion-to-normal (L/N) uptake ratio. One hundred twenty-five patients suffered from neoplastic lesions and seventeen patients harboured an non-neoplastic lesion. The neoplastic lesions were also classified as high and low grade. There was a statistical significant difference between L/N values of neoplastic and non-neoplastic lesion. In gliomas, 99mTc-TF showed promise for the differentiation of glioma recurrence from radiation necrosis, neoplastic from non-neoplastic intracerebral hemorrhage and for the assessment of glioma aggressiveness. Furthermore, in glioblastoma we found that patients with high preoperative L/N tracer uptake had significantly worse survival. In meningiomas, 99mTc-TF could aid the discrimination between typical and anaplastic meningiomas. CONCLUSION: 99mTc-TF brain SPECT can provide important information over the nature of an intracranial space occupying lesion and should be included in the armamentarium of available diagnostic imaging studies for the evaluation of intracranial lesions. The lower cost and greater availability of SPECT is another important factor.

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P.060. CORTICAL HEMOSIDERIN IS A RISK FACTOR FOR SEIZURES IN PATIENTS WITH NEWLY DIAGNOSED BRAIN TUMORS

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BACKGROUND: Hemorrhage is common in brain tumors. Due to the characteristic magnetic field changes induced by hemosiderin it can be detected using susceptibility weighted MRI (SWI). It's relevance to clinical syndromes is unclear. Here we investigated the patterns of intra-tumoral SWI positivity (SWI_{pos}) with regard to the prevalence of epilepsy. PATIENTS AND METHODS: We retrospectively selected 105 patients with newly diagnosed supra-tentorial gliomas and brain metastasis. Oligodendroglial tumors which frequently show SWI_{POS} due to calcification were excluded. Patient charts were reviewed for the presence of seizures and medication. The following parameters were recorded from pre-operative MRI: (1) SWI_{POS} as defined by dot-like or fine linear hypointense signal changes not to be attributed to flow signal from vessels; (2) allocation of SWI_{POS} to the tumor compartments of contrast enhancement, central hypointensity, or periphery outside the enhancing zone; (3) allocation of SWI_{POS} to include the cortex, or SWI_{POS} in subcortical tumor parts only; (4) tumor size on gadolinium-enhanced T1 and T2 weighted images. RESULTS: 80 tumors (76%) showed SWI_{POS} (4/14 diffuse astrocytoma WHO II, 5/9 anaplastic astrocytoma WHO III, 41/46 glioblastoma WHO IV, 30/36 metastasis). The presence of SWI_{POS} depended on tumor size ($p < 0.0005$) but neither on patient's age, nor on medication with antiplatelet drugs or anticoagulation. In 89% SWI_{POS} was located to the contrast-enhancing or central tumor part. Seizures occurred in 60% of patients. In SWI_{POS} tumors seizures were highly associated with the presence of cortical SWI_{POS} ($p = 0.0026$). Interpretation: Cortical SWI_{pos} confers a risk for seizures in newly diagnosed brain tumors. The different patterns of intra-tumoral SWI_{pos} distribution may reflect distinct pathophysiological pathways associated with vascular pathology and tumor necrosis. Whether development of cortical SWI_{pos} induced by treatment or by the natural course of non-hemorrhagic tumors leads to the new onset of seizures has to be addressed in longitudinal studies.

P.061. THE EVALUATION OF THE BRAIN INFARCTION AFTER GLIOMA SURGERY USED BY MRI DIFFUSION WEIGHTED IMAGE

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OBJECTIVE: MRI diffusion weighted image(DWI) was performed to evaluate the postoperative complications of cerebral infarction in glioma. METHODS: During August 2010 from April 2009, at our hospital, MRI DWI was performed postoperatively in 20 patients who underwent initial glioma surgery at our hospital(Male10, Female10, mean 58.3y/o). Grade glioma patients were 4 cases WHO grade II, 3 cases were WHO grade III and 13 cases were WHO grade IV. Tumor localization, 7 cases of frontal lobe, 4 cases of temporal lobe, parietal lobe 6 cases, one case of occipital lobe, 2 cases of insular gyri. The tumor diameter were 8 cases more than 5cm (Large size), 3～5cm were 7 cases(Middle size), 3cm or less were 5 cases(Small size). Using a 1.5 Tesla MRI made by SIEMENS. MRI Gd enhanced, T1WI, T2WI, FLAIR, T2* and DWI as a preoperative examination were performed. And cerebral angiography was performed in all patients. DWI before surgery is performed because there is a high signal due to the high cell density. MRI DWI, T1WI and Gd enhanced were performed within 48 hours after removal of the resected glioma. RESULTS: Removal rate were Gross total removal of 4 cases, subtotal removal of 7 cases and partial removal of 9 cases. Postoperative brain infarction occured 15 cases. Small cerebral infarction (less than 1cm) occurred in 12 cases. Middle cerebral infarction occurred in 3 cases. The positive rate of MRI DWI was 75%. WHO Grade II, III was less infarction merger cases. The relationship between tumor size and MRI DWI positive rate was poor. In cases that occurred tumor stain, Early vein is in many cases angiography was infarct has occurred. CONCLUSION: High-grade glioma vessel construction is weak, brain infarction occur during the glioma surgery. Abnormal vascular structure is often the cause of cerebral infarction.

P.062. SIGNS OF WALLERIAN DEGENERATION OCCUR WITHIN WEEKS FOLLOWING BRAIN TUMOR SURGERY-RELATED ISCHEMIC STROKE

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BACKGROUND: Wallerian degeneration (WD) is characterized by axonal degeneration and demyelination following injury to the CNS. Due to the enlargement of the extracellular space WD results in hyperintense T2 signal changes along the corticospinal tract on MRI and ipsilateral brainstem atrophy. To date not much is known about the time course of such changes in patients with brain tumors. METHODS: In an ongoing retrospective study we reviewed the charts and analyzed the pre- and post- operative MRI of patients with supra-tentorial brain tumors which were diagnosed with post-operative WD of the corticospinal tract. We identified three WD patients which developed hemiparesis consecutive to a surgery-related stroke of the middle cerebral artery territory. We analyzed the MRI by searching for typical hyperintense signal changes within the ipsilateral corticospinal tract of the brain stem. We also measured the ipsi (ILAT)- and contra (CLAT)- lateral brain stem area on T2-weighted images and calculated an asymmetry index as a measure of hemiatrophy ($AI = 100*(ILAT-CLAT)/(ILAT + CLAT)$ [%]). Results were then compared with the extent and time course of the contralateral motor weakness. The motor score of the paretic side equals the sum of the proximal and distal upper and lower limb muscle strength (normal motor score: 20 points, hemiplegia: 0 points). For control we analyzed the MRI of six patients not suffering from post-operative WD and hemiparesis and measured the AI of the brainstem. RESULTS: Pre-operatively no MRI revealed signs of WD and no patient showed any motor deficit. In the post-operative MRI of the three WD patients (two glioblastoma, one meningioma) hyperintense signal changes in T2-weighted images within the ipsilateral corticospinal tract descending from the cerebral peduncle through the pons and medulla oblongata together with a hemiatrophy of the brainstem were detected. These changes occurred as early as 1.5 months after surgery and persisted during the whole follow-up period (3.4 to 27.6 months). The mean AI of WD patients increased from 0.3% (range: -0.3 to 0.7%) prior to surgery to 9.4% (range: -7.1 to -10.3%) after surgery (mean 13.5 months). All WD patients developed contralateral motor deficits with a post-operative decline of the motor score by 8 to 13 points. Neither the imaging changes nor the functional deficits improved over time. In the control group the mean AI was 0.1% (range: -1.81 to 0.97%). CONCLUSION: MRI signs of WD develop within a few weeks after stroke due to brain tumor surgery. WD is associated with persisting motor deficit. The hyperintense MRI changes typical for WD must not be confounded with tumor progression or tumor induced edema respectively. Whether corticospinal compression or infiltration by the tumor itself can cause WD is under investigation.

P.063. PERINEURAL TUMOR SPREAD - INTERCONNECTION BETWEEN SPINAL AND CRANIAL NERVES

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INTRODUCTION: Cranial nerves are often involved in patients with head and neck malignancies. Malignant tumors of the parotid gland usually involve the facial nerve, while involvement of the mandibular nerve is commonly seen in nasopharyngeal carcinoma. The secondary neoplastic involvement of the spinal nerves in patients with head and neck malignancies is extremely rare. METHODS: A fifty-seven year-old patient was operated and irradiated due to squamous cell carcinoma of the tongue base. Three years later the patient complained of the right shoulder pain, while 16 months after, magnetic resonance imaging (MRI) of the brain and neck was ordered because of severe and sustained right facial pain, lasting for several months, predominantly involving the right ear. RESULTS: No abnormalities were seen within the brain parenchyma. MRI of the neck revealed the presence of the soft tissue neoplastic infiltration of the right C2 root, with distal involvement of the great auricular nerve, associated with perineural tumor spread to the facial nerve. No local recurrence of the tongue base cancer was noted. DISCUSSION: Best of our knowledge, this is the first reported involvement of the cervical plexus in patients with head and neck cancers associated with the clearly documented interconnection between the cervical plexus and cranial nerves via great auricular nerve. This nerve is the largest among the superficial ascending branches of the cervical plexus,

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winds around the posterior border of the sternocleidomastoid muscle and after perforating deep fascia divides into anterior and posterior branch. The anterior branch inervates the skin over the parotid gland and communicates with the facial nerve.

P.064. MULTIFOCAL EXTRADURAL AND INTRADURAL EOSINOPHILIC GRANULOMA IN AN ADULT

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INTRODUCTION: Eosinophilic granuloma is a type of histiocytosis X that is a benign bone tumor. Multifocal extradural and intradural involvement in adults is extremely uncommon, as 90% of cases occur in male children under the age of 10 years. The etiology of this disease is unknown, but it occurs with the accumulation of eosinophils and histiocytes in the medullary layers of the bone. The beginning of the inflammatory process in the dural membrane after migration of Langerhans cells may result in intradural involvement and sinus invasion into the nearby tissue. For multiple bone lesions, the use of chemotherapy, radiotherapy, and systematic cortisone is effective. In this study, we discuss the case of a 44-year-old male patient admitted to our clinic with sinus invasion and multiple painful cranial swellings. CASE: A 44-year-old patient visited our clinic with multiple cranial swellings accompanied by pain. There were no pathological findings on systemic or neurological examination. Findings of biochemical and microbial examination were normal, and scans revealed no evidence of metastasis. Magnetic resonance imaging showed intense contrast enhancement of a mass measuring approximately 5.5 × 1.5 cm. This mass was causing destruction of the right parietal tabula and extended to the adjacent dural surfaces. It was concluded that the mass was compressing the right transverse-sigmoid sinus junction. Furthermore, lesions with similar signal density were observed at the right frontal region (measuring 3 × 1.7 cm) and in the left temporal region (measuring 4 × 1.2 cm); these lesions caused destruction of the tabula and extended to the adjacent dura (Figure 1). The mass at the right parietal lobe was excised along with the surrounding intact tissue for diagnosis and treatment purposes. The mass had caused a periost reaction, had eroded the bone, and was spreading outside the cranium. After removal of the mass, the dura was found to be intact (Figure 2). The patient was treated with low-dose cortisone and analgesic. After surgery, the patient's pain was dramatically alleviated. As there was no systematic involvement or neurological deficits, further treatment, such as RT and chemotherapy, were not required (Figure 3). DISCUSSION: Eosinophilic granuloma is a localized form of histiocytosis X that occurs in children and young adults. Generally, in these cases, a single lesion is detected and cranial and vertebral bone involvement may be identified in addition to long and flat bone involvement. More common symptoms include pain, swelling, fever, and leukocytosis. Pain in the lesion area develops as a result of expansion of the medullary bone. Neurological symptoms may occur due to compression caused by bone destruction. Single lesions can be treated effectively with surgery and local cortisone infusion, and multiple bone lesions and systemic involvement are treated with chemotherapy and radiotherapy (RT).

P.065. FOREIGN BODY GRANULOMA MIMICKING RECURRENT INTRACRANIAL TUMOR

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Gelatin sponge, oxidized cellulose and microfibrillar collagen are used to achieve hemostasis during neurosurgical procedures. Hemostatic agents may produce clinically symptomatic, radiologically apparent mass lesions. The differential diagnosis should include the foreign body along with recurrent tumor. We present a case of intracranial hemostatic agents found in a 56-year-old male patient seven years after undergoing a craniotomy for a left posterior parietal convexity meningioma. Preoperative magnetic resonance imaging suggested the presence of a recurrent tumor. We emphasize that although it is rare, a granuloma due to a foreign body reaction can result in a false image of tumor recurrence. CASE: A 56-year-old man had previously undergone resection on a left parietal convexity meningioma at another institution. Seven years later, he was admitted to our institution with the complaint of headache, right hemiparesis, and seizures. Tl-weighted, T2-weighted, and magnetic resonance imaging demonstrated an enhancing mass in the resection cavity, which was suggestive of a recurrent tumor (Fig. 1A and 1B). In addition, there was evidence of a previous craniotomy with an adjacent left posterior-parietal lobe encephalomalacia (Fig. 2). It was believed that the mass might be a foreign substance or relapsed meningioma, and as a result, the patient was operated upon. During the craniotomy, it was observed that the mass was a sponge with surrounding granulation tissue. During surgical exploration, the tumor was determined to be globular, partly lobulated, hard, and well demarcated. The sponge and surrounding granulation tissue were removed. A sample taken from the surrounding tissue was analyzed in terms of histopathology. Consequently, a foreign substance reaction and chronic inflammation were identified. The postoperative condition of the patient was good, and he did not suffer any attacks. No new mass was identified following control computerized tomography examination (Fig. 3). DISCUSSION: Hemostatic agents are widely used in neurosurgery to aid in hemostasis. They may cause a foreign body reaction, which appears on MR images as identical to recurrent tumor. Clinical symptoms caused by foreign body granuloma may appear months or even many years after a surgical procedure. Although reasonable care is shown in this matter, there are rare cases where these pads are forgotten in the surgical area. This results in chronic inflammation characterized by foreign substance reaction and granuloma formation. Granulomas of the foreign body type following neurosurgical procedure are very rare. Cotton materials commonly used for hemostasis may cause a granulomatous reaction that may mimic recurrent. or progressive neoplasm or abscess on postoperative imaging studies. In patients with a history of craniotomy, cotton granuloma should be considered in the differential diagnosis.

P.066. BEVACIZUMAB-INDUCED CALCIFIED NECROSIS IN GLIOBLASTOMA PATIENTS: NEURORADIOLOGIC AND HISTOLOGICAL FEATURES AND PROGNOSTIC VALUE

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Therapy-induced calcifications in glioblastoma patients are rarely recognized. Recently, we reported on the frequent occurrence of hyperintense lesions on T1 precontrast MRI in glioblastoma patients exposed to bevacizumab. These T1 hyperintense areas corresponded to hyperdense lesions with characteristics of calcifications on CT scans and their occurrence was predictive of a better response towards bevacizumab. Briefly, in 22 of 36 sequentially treated patients (61.1 %), T1 hyperintense lesions became apparent 55 days (median) after bevacizumab treatment. CT scans, available in 14 of these 22 patients (63.6%), showed focal tumor calcifications. Patients with therapy-induced T1-hyperintense lesions had better progression-free survival and overall survival compared to patients without these changes (median 5.8 vs. 3.5 months and 9.7 vs. 5.0 months, respectively). There was a striking correlation between the appearance of therapy-induced T1 hyperintense lesions and objective responses to bevacizumab. One of the patients with T1 hyperintense lesions developed atypical progressive changes on MRI while receiving bevacizumab. An image-guided stereotactic biopsy was performed with tissue sampling on multiple levels. MR findings, CT findings and tissue analysis were matched with the aid of the BrainLab software. T1 hyperintense lesions corresponded to mainly necrotic areas with extensive mineralization as detected by histological analyses using alizarin red staining. Vital tumor was only found in regions corresponding to T1 non-hyperintense areas on MRI with varying degrees of T2 hyperintense signals and contrast enhancement. Calcified areas on CT closely matched T1 hyperintense lesions and necrotic areas with mineralization. In summary, T1 hyperintense lesions seem to be common in glioblastoma patients treated with bevacizumab and may serve as a biomarker of response and outcome. Our neuroradiologic and histologic findings suggest that these therapy-induced T1 hyperintense lesions correspond to tumor calcifications. In addition, the mutually exclusive pattern of calcified necrosis in T1 hyperintense areas and vital tumor only in neighboring sections is intriguing. These findings have implications for the interpretation of MR and CT scans and should also be considered when tissue sampling by stereotactic biopsy is planned in patients previously exposed to bevacizumab.

P.067*. NON-INVASIVE ASSESSMENT OF THE INVASIVE MICROENVIRONMENT OF GLIOBLASTOMAS: A MULTI-MODAL IMAGING STUDY

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INTRODUCTION: Invasion of local white matter is a key pathological hallmark of glioblastomas (GBM) and the major cause of treatment failure. Our understanding of invasion, largely from animal studies, has shown it involves multiple pathological processes. Little has been done in human patients as we cannot identify the invasive region with conventional MRI. New MR methods allow assessment of pathological changes that occur at a scale below the voxel resolution. Our work with diffusion tensor imaging (DTI) has shown that it can identify this invasive region and predict patterns of tumour recurrence. In this study we have used MR perfusion and spectroscopy to assess the invasive microenvironment of this DTI-defined invasive region. METHODS: 40 patients with glioblastomas (mean age 55, range 28-75; 28 male) were imaged preoperatively at 3T (Seimens TrioTim) with conventional MR, DTI, perfusion MR and multivoxel MR proton spectroscopy (TE = 35 ms). The processed data sets were coregistered and the invasive region defined from the isotropic (p) and anisotropic (q) components of the diffusion tensor. Measurements of rCBV and metabolite concentrations from MRS were made in the invasive region, non-invasive and contralateral hemisphere. RESULTS: rCBV in invasive regions was significantly higher than in non-invasive regions (mean 3.3 vs 2.1; $P = 0.001$) suggesting increased vascular density and angiogenesis in these areas. Spectroscopy data identified 17 metabolites, but seven in sufficient numbers to analyse. MRS showed that in invasive areas there is a significant decrease in NAA (a marker of intact neurons), myoinositol (a marker of glial viability) and glutamate (a marker of the intact glial-matrix) without any increase in choline (cellular proliferation) or lactate (hypoxia). Comparisons between normal-appearing and contralateral white matter demonstrated no difference. CONCLUSION: Multimodal MR imaging of invasive regions can identify pathological changes that correspond to our understanding of the process of glioma invasion. It will provide a non-invasive method of assessing invasion in individual patients and should allow monitoring of novel anti-invasive therapies.

P.068. THE IMPORTANCE OF LATENCY CORRECTION FOR NEURONAVIGATED TRANSCRANIAL MAGNETIC STIMULATION (NTMS) MAPPING, ESPECIALLY OF THE FACE AND TONGUE AREA: A TECHNICAL NOTE

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Presurgical functional brain mapping is important for optimized resection planning of eloquently located brain tumors of the primary motor region. Beyond functional MRI (fMRI), motor mapping by navigated Transcranial Magnetic Stimulation (nTMS) has attracted rising attention in the last years. Facial and tongue mapping by nTMS is often limited by direct stimulation effects of facial and trigeminal nerve fibres. Short latency MEPs recorded during the mappings may lead to false-positive results. We therefore analyzed MEP latencies in a preclinical trial and investigated the effect of latency-correction in presurgical, clinical mappings. We examined 10 healthy, right-handed subjects on three days by single pulse nTMS (eXimia 3.2.2; surface electrode MEP recordings: abductor pollicis brevis muscle [APB], plantaris muscle [PM], orbicularis oris muscle [OO], mentalis muscle [MM] and tongue; stimulation at 110% of resting motor threshold [RMT] over primary motor corex; if the RMT could not be determined due to direct stimulation effects, mapping was performed at 95% of MT and muscular pre-contraction). In addition to the preclinical setup, we analyzed the effect of latency correction in presurgical mappings of the tongue and face area in patients with eloquently located brain tumors. Latencies directly correlated with human height, mostly for PM mapping. Mean latencies +/- 1SD were 23 +/- 2ms for APB, 44 +/- 4ms for PM, 10.8 +/- 0,6ms for MM, 11.0 +/- 0.5ms for OO and 9.7 +/- 0.8ms for the tongue. According to literature, we regarded latencies below 7.0ms as direct stimulation artifacts. Mapping of the perioral region was feasible in 8/10 subjects only, interfered by direct stimulation effects. The mean latencies were independent from muscular pre-contraction (mean latencies [N = 21 each]: MM at rest 10,69ms, MM pre-contracted 11,03ms, OO at rest 11,33ms, OO pre-contracted 10,96ms). Without latency correction, false-positive stimuli due to direct stimulation effects were recorded, especially when stimulating over the frontolateral cortex/perional region. NTMS mapping of the facial and tongue muscles is technically rather difficult. It often requires muscular pre-contraction to lower excitability thresholds. Direct facial nerve stimulation effects often interfere with cortical TMS effects. We suggest to use latency correction (7.0-16.0ms for tongue/face mapping, independent from pre-contraction, height or age).

P.069. MAPPING OF THE PERIORAL REGION BY NEURONAVIGATED TRANSCRANIAL MAGNETIC STIMULATION (NTMS): MENTAL MUSCLE SUPERIOR TO ORBICULARIS ORIS MUSCLE FOR MEP RECORDINGS - A TECHNICAL NOTE

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Functional brain mapping is an important presurgical tool for optimized resection planning of eloquently located brain tumors. In addition to functional MRI, motor mapping by navigated Transcranial Magnetic Stimulation (nTMS) has been established for clinical routine in the last years. Facial mapping by nTMS is often limited by direct stimulation effects of facial and trigeminal nerve fibres. This direct effect is dose-dependent; thus, stimulating at the lowest amplitudes possible should be intended. We therefore compared the most frequently used muscles for mapping of the mouth area, i.e. mental muscle and orbicular oris muscle concerning test-retest-reliability and feasibiltiy. We examined 11 healthy subjects on 3 different days within 6 weeks by single pulse nTMS using eXimia 3.2 for simultaneous mapping of orbicular oris muscle (OO) and mental muscle (MM). Registration mismatches >3mm were not accepted. MEPs were recorded by surface EMG electrodes and lateny-corrected (latencies accepted from 7-16ms). Stimulation was primarily performed at rest, at 110% output compared to the resting motor threshold of the corresponding area [RMT]; if the RMT could not be determined due to direct stimulation, mapping was performed at 95% of direct motor threshold with muscular pre-contraction. Facial mapping of the mouth was feasible in 8/11 subjects. In 3/11 subjects reproducible mapping was not possible due to direct stimulation effects. The mean latency was 10-11ms, independent from muscular pre-contraction (21 investigations at rest/21 investigations at pre-contraction; mean latency MM at rest 10.69ms, MM pre-contracted 11.03ms, OO at rest 11.33ms, OO pre-contracted 10.96ms). Stimulating both muscles simultaneously, the RMT was usually lower for mental muscle (75% of cases), the number of positive stimuli (amplitude >50uV) was significantly higher using mental muscle (mean/session: MM 380 stimuli/OO muscle 273 stimuli) and the mean amplitude was higher (MM: 458uV/OO: 342uV). Intersession reliability was comparable. Presurgical mapping of the perioral region by nTMS was feasible in 75% of healthy subjects. The mentalis muscle mapping seems to be technically superior to orbicularis oris muscle mapping but still often requires muscular pre-contraction.

P.070. TEST-RETEST RELIABILITY OF PRIMARY MOTOR CORTEX MAPPING: NEURONAVIGATED TRANSCRANIAL MAGNETIC BRAIN STIMULATION (NTMS) VERSUS FUNCTIONAL MRI (FMRI)

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Presurgical functional brain mapping is essential for optimized resection planning of eloquently located brain tumors. Functional magnetic resonance imaging (fMRI) has been the most established method for presurgical motor mappings but was shown to have a rather low test-retest reliability, especially for the face and tongue area. Recently, neuronavigated Transcranial Magnetic Stimulation (nTMS) has attracted rising attention as an alternative motor mapping method applicable for clinical routine. Anyway, little was known about the reliability of nTMS. Thus, we compared the reliability of both motor mapping approaches in a preclinical trial. We examined 10 healthy, right-handed subjects on three days (d0, d3-5, week 3-5) by nTMS (eXimia 3.2.2, 110% of resting motor threshold on dominant primary motor cortex, MEP recordings: abductor pollicis brevis muscle, plantaris muscle, perioral muscles, tongue) and fMRI (Siemens 3T Trio, motor paradigms: [1] bilateral thumb abduction, [2] unilateral toe flexion, [3] pursing lips, [4] tongue abduction). Euclidean distances (ED) between hotspots and centers of gravity (CoG) of the three mapping sessions were calculated. Spatial reliability was tested by intersession overlaps and voxel-wise interclass correlation (ICC). Overall, the mean ED of the hotspots was higher for nTMS (10.77 $\pm$ 1.88mm) as compared to fMRI (6.2 $\pm$ 1.1mm), whereas there was no difference in ED of the CoGs (mean 6.7mm). Regarding the spatial reliability (i.e., overlap volumes and ICC), nTMS was superior for hand and foot mappings but not for perioral and tongue mappings. The cortical representation of the perioral showed a broad overlap with the tongue area in both assessments. CoGs were similarly reproducible by fMRI and nTMS. Both methods seem sufficiently reliable for clinical application. In terms of spatial reliability, nTMS seems to be superior to

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map the primary motor areas of hand and foot but less accurate for lips and tongue. Thus, both methods may well complement each other in the clinical routine.

P.071. THE FUNCTIONAL DIFFUSION MAP (FDM) IN DIFFUSE INTRINSIC PONTINE GLIOMAS (DIPG)

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INTRODUCTION: The functional diffusion map (fDM) has been suggested as a tool for early detection of tumour treatment efficacy. The fDM compares pre- and post-treatment apparent diffusion coefficient (ADC) maps in diffusion-weighted MRI (DWI). An increase in ADC is said to reflect a decrease in tumour cellularity and a good treatment response. A decrease in ADC is said to reflect an increase in tumour cellularity and a poor treatment response. To our knowledge the behaviour of the fDM in diffuse intrinsic pontine gliomas (DIPG) has not been examined. METHODS: 18 patients with DIPG, and who had DWI as part of their clinical imaging, were enrolled in a retrospective study. The fDM was used to compare baseline pre-treatment ADC maps with ADC maps obtained between 2 weeks and 9 months post-treatment. The percentage area with increased, no change, and decreased ADC was calculated within tumour areas. We noted that in our patient group the tumour area consisted of, on average, 11.2% necrosis. Hence, we analysed the fDM both including and excluding areas of necrosis, as well as in necrotic areas alone. RESULTS: In this cohort, 16/18 patients died within an average period of 9 months (minimum 5 months, maximum 2 years). When necrotic regions were included, the fDM showed no change in ADC pre-and post- treatment as the major result in 15/18 patients, a decrease in ADC in 2 patients and an increase in ADC in 1 patient. When excluding areas of necrosis, the major result was no change in ADC in 16/18 patients and a decrease in ADC in the remaining 2 patients. Although the overall change was not markedly different, when comparing the two methods there was a statistically significant difference in the results when including and excluding necrotic areas ($p < 0.05$). Analysing areas of tumour necrosis indicated that the major change in ADC was an increase in ADC in 11 patients, no change in 3 patients and a decrease in ADC in 9 patients. This was invariably related to an increase or decrease in necrotic tumour volume. DISCUSSION: In agreement with literature relating to treatment outcome of patients with DIPG, as well as the outcome of this cohort, our results have shown that the fDM, excluding areas of necrosis, showed that treatment given to these patients was ineffective in all cases. Furthermore we have identified areas of necrosis as a potential confounder in the fDM. To our knowledge the behaviour of the fDM in necrotic regions of tumour has not been examined. We note that necrotic areas of a tumour can increase in size both as a result of successful treatment (as cells are killed, tumour regions are replaced by areas of necrosis), and as a result of tumour growth (causing increased hypoxic regions and hence necrosis). Apart from indicating the known ineffectiveness of current treatments of DIPG, our results also show that post treatment fDM analysis of childhood DIPG requires the removal of necrotic areas to accurately assess tumour response.

P.072. SUSCEPTIBILITY CHANGES IN MENINGIOMAS INCREASE THE MEAN APPARENT DIFFUSION COEFFICIENT IN DIFFUSION WEIGHTED MRI

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BACKGROUND: Diffusion weighted magnetic resonance imaging (DWI) provides information of water diffusivity which is expressed by the apparent diffusion coefficient (ADC). In gliomas it has been shown that ADC values correlate with tumor cell density and allow early treatment response assessment. At the present time it is not known which biological aspects of meningiomas are reflected by their behavior in ADC images. Further it is not known whether intra-tumoral susceptibility changes alter ADC values. In susceptibility-weighted MRI (SWI) the hypointense changes (SWI_{pos}) in meningiomas can be associated with intra-tumoral calcification. Here we analyzed whether intra-tumoral SWI_{pos} influences ADC values in untreated meningiomas. METHODS: Retrospectively pre-operative SWI and DWI of patients ($n = 20$, 60 ± 15yrs; mean $\pm$ SD) with newly diagnosed meningiomas were analyzed. We grouped our patients into meningiomas with substantial intra-tumoral SWI_{pos} ($n = 10$) and SWI negative meningiomas ($n = 10$). SWI_{pos} was defined as dot-like or fine linear hypointense signal changes not to be attributed to flow signal from vessels. ADC values were calculated based on region of interest (ROI) analysis. ADC values of SWI_{pos} and negative meningiomas were compared. RESULTS: The mean age of patients with SWI_{pos} meningiomas was higher (66 ± 12yrs) when compared to patients with SWI negative meningiomas (53 ± 15yrs). The mean ADC values in SWI_{pos} meningiomas were higher (1.13 ± 0.29 $x10^{-3}mm^2/s$) compared to SWI negative meningiomas (0.83 ± 0.08 $x10^{-3}$ mm^2/s; $p < 0.01$). In those patients where SWI phase images were available, SWI_{pos} could be attributed to possible calcification based on the phase shift ROI analysis. CONCLUSION: SWI_{pos} in meningiomas influences DWI results by increasing ADC values on average by 35%. The frequency of SWI_{pos} in elderly patients is in line with the known age-associated calcification in meningiomas. The shift of ADC values due to susceptibility changes needs to be considered when drawing conclusions on tumor behavior from DWI.

P.073. MINKOWSKI FUNCTIONAL IMAGE ANALYSIS ALLOWS PSEUDOPROGRESSION TO BE DIFFERENTIATED FROM PROGRESSION IN BRAIN TUMOURS

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INTRODUCTION: Pseudoprogression (PsP) of glioblastoma describes false positive progressive disease within 6 months of treatment. This is typically determined by MacDonald MRI criteria, which are based on non-specific interval changes in contrast enhancement on T_1-weighted images. It is only in the unusual situation that new enhancement occurs outside the radiation field that progression and PsP can be distinguished with conventional MRI. PsP can confound response assessment and any imaging technique that reliably distinguishes responders to treatment from non-responders at an early stage will allow more rational treatment administration. OBJECTIVE: The objective of this study was to differentiate PsP from progression based on the assertions that (1) tissue morphology is a sensitive indicator of underlying biology and (2) that morphological information can be extracted from pixels in the MR image. METHODS: T_2-weighted MRI data were obtained from 50 patients, the tumour region of interest segmented, the pixel grey-scale thresholded, and pixels assigned black or white at each threshold. 2D Minkowski Functionals (MFs) allow characterisation of morphological heterogeneity using the parameters area, perimeter and genus. MFs were obtained from the thresholded images. RESULTS: Blinded analysis was initially performed in all patients with progression, PsP, stable disease and partial response. Outlier analysis showed MFs are likely to be sensitive to MRI field strength. Principal component analysis (PCA) demonstrated that MFs are insensitive to the potential confounders of age, Karnofsky Performance status, location, pre-operative tumour size, treatment compliance and extent of debulking. PCA also determined which thresholds contributed the most to MF variance. When these thresholds were plotted against time, subsets of heterogeneity within patients emerged. A mixed model demonstrated an increase in heterogeneity after treatment supporting the use of this biomarker in subsequent unblinded, supervised analysis. MF values of progressors and PsPs separated over time with progressors becoming more heterogeneous. Critically, separation was seen at the clinically relevant time point of 4 months ($P < 0.05$, 2-way RM ANOVA; Bonferroni). Feature selection using t-tests set at $P < 0.05$ and subsequent cross-validated support vector machine classification cleaved the groups apart with 94% accuracy at 4 months. We tested those with stable disease with this classifier and achieved 100% accuracy. Inter-observer agreement for MF-based classification following segmentation was 100%. CONCLUSIONS: We have shown that using T_2-weighted MRI data alone, which is acquired routinely in the clinic, the important phenomenon of PsP can be distinguished from progression. We achieved this by capturing information on underlying tumour heterogeneity that is not apparent to the reporting radiologist.

P.074*. DYNAMIC SUSCEPTIBILITY CONTRAST PERFUSION MRI IN DIFFERENTIATING RADIATION NECROSIS FROM TUMOR RECURRENCE IN HIGH-GRADE GLIOMAS

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OBJECTIVES: We investigated perfusion magnetic resonance imaging (MRI) in the assessment of glioma progression and radiation necrosis following tumor resection, radiation therapy and chemotherapy in patients with

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high grade glioma. METHODS: Twenty-six previously resected and irradiated patients with high-grade gliomas proven by histology (10 grade III and 16 grade IV) were examined. Twenty-seven structural lesions with blood-brain barrier disruption were detected by magnetic resonance imaging (MRI). All patients presented with clinical symptoms suggestive of brain tumor recurrence or necrosis after radiotherapy. Dynamic susceptibility contrast perfusion MRI (DSCE) was applied to differentiate necrosis and progression. The median follow-up was 6.5 months. For quantitative analysis, we employed region based (ROI) relative cerebral blood volume (rCBV) analysis averaged over the ROIs. Contralateral white matter was used as a reference to calculate an asymmetry index, AI ($rCBV_{tumor} - rCBV_{control}$)/($rCBV_{tumor} + rCBV_{control}$). CBV image processing and analysis were performed with the NordicICE 2.3.12v software (NordicNeuroLab®). RESULTS: There were highly significant rCBV differences between the tumor recurrence group (7.71 $\pm$ 3.41, mean $\pm$ standard deviation) and the radiation necrosis group (3.56 $\pm$ 2.46; $p = 0.001$). Enhancing lesions with an AI of an rCBV values that exceed ≥ 3.7 are indicative of tumor recurrence with a sensitivity of 90% and a specificity of 63%, according to the ROC analysis (AUC 0.84, 95% confidence interval 0.7 – 0.96). In the tumor recurrence group six out eleven patients underwent surgical resection that confirmed recurrence. In the radiation necrosis group two out 16 patients underwent open biopsy through the previous craniotomy showing only radiation necrosis without any evidence of recurrence. CONCLUSIONS: MR perfusion imaging offers an addition to structural MRI approaches in the differentiation between radiation necrosis and tumor progression.

P.075*. PERFUSION COMPUTED TOMOGRAPHY IN THE EARLY EVALUATION OF THE RESPONSE TO BEVACIZUMAB TREATMENT IN HIGH GRADE GLIOMAS

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PURPOSE: to evaluate if early perfusion changes during treatment may be predictive of response to antiangiogenic therapy in high grade gliomas utilizing Perfusion Computed Tomography (PCT). MATERIALS AND METHODS: PCT was performed in 15 patients by using a 128-section multidetector-row scanner. Each patient underwent two PCTs: a pretreatment (baseline) examination and an intra-treatment examination immediately before the second dose of the drug. Parametric Cerebral Blood Volume (CBV) maps were generated by a commercially available workstation; while the quantitative analyses of the perfusion maps, based on voxel-by-voxel information, were performed using an in-house software. An expert radiologist identified the lesions both on post-gadolinium T1-weigthed and on fluid-attenuated inversion recovery (FLAIR) Magnetic Resonance (MR) images. A semiautomatic segmentation algorithm was used to delineate the regions of interest (ROIs). Co-registration between CBV maps and MR images was performed to allow the identification of the same ROIs on the perfusion images. The histograms of the CBV values derived from the two PCTs were then compared. The clinical response was assessed according to RANO criteria, based on MR imaging follow-up at two months after the start of the therapy. Correlations between these results and perfusion changes were evaluated by using statistical tests. RESULTS: Perfusion changes resulted in agreement with follow-up morphological MR imaging, anticipating, in the majority of cases, the post-gadolinium T1-weigthed and FLAIR volume modifications. All patients considered as not responding, because showing increased hyperperfused volumes, also exhibited both an increasing contrast-enhancing and non-enhancing lesions; patients having almost unchanged CBV histogram, also showed stable lesions on MR images; those considered as responding, because characterized by a marked reduction in CBV values, also showed decreased contrast-enhancing and non-enhancing volumes. Only in one case, a patient exhibited an increased CBV, with an increasing non-enhancing lesion but a decreased contrast-enhancing component at follow-up. CONCLUSION: PCT showed a great ability to identify early tumor-specific changes that may be predictive of the response to therapy. Larger trials are needed to better understand the mechanisms of action of bevacizumab and their correlation with data derived from perfusion imaging.

P.076*. A NOVEL DIFFUSION TENSOR MR BASED APPROACH TO EVALUATE STRUCTURAL FEATURES OF LOW-GRADE GLIOMAS

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INTRODUCTION: This study aimed at evaluating a new segmentation technique based on diffusion tensor decomposition into an isotropic (p) and an anisotropic component (q) to better characterize the tumour tissue heterogeneity. In addition, enabling a voxel-by-voxel analysis, this technique allow the depiction of parametric changes between two distint studies performed at distinct timepoints. In particular, to characterize the structural heterogeneity of low-grade-gliomas (LGGs), we aimed at: i) comparing the images obtained from the p:q decomposition with the dataset acquired with FLAIR sequences; ii) correlating the results of segmentation with histopathological findings from image-guided tumour biopsies; iii) evaluating the evolution of a given lesion throughout time, when applicable, and comparing distinct imaging behaviour with neurophysiologic intraoperative data. PATIENTS & METHODS: p and q maps were obtained from diffusion-tensor-acquisitions in 50 patients with primary LGGs. They were fused with DTI-FT reconstruction and volumetric FLAIR and post-GdT1-weigthed images, loaded into the neuronavigation system, to be available intraoperatively. RESULTS: p map depicted a tumour area larger than that detected in FLAIR images. The tumour ROI on q maps was located inside the area depicted on p maps. The structural heterogeneity of p and q maps did not match with the degree of heterogeneity shown by FLAIR images, or with areas of contrast enhancement. Samples taken in p areas always revealed the presence of a LGG; samples in p areas located externally to the border depicted in FLAIR images and within p maps, were classified as infiltrative areas of LGG. Samples external to p areas was normal brain parenchyma; Samples in q areas showed regions of highly compacted tumour cells, and in tumours in which p and q maps did not match, the area of q maps showed foci of anaplasia. P:q maps also correlated with different molecular profile (MGMT status, 1p19q deletion, IDH-1 status). When applicable, neurophysiologic changes in stimulus threshold well correlated with the degree of changes depicted by p:q functional maps. CONCLUSION: p and q maps better correlate with the degree of LGG heterogeneity than conventional MR images; this data has potential clinical implication for sampling for histological and molecular diagnosis and for better quantify the response to a given treatment over time.

P.077*. RADIOGRAPHIC DIAGNOSIS OF PSEUDOPROGRESSION AND CORRELATION WITH SURVIVAL OF PATIENTS WITH GLIOBLASTOMA AFTER CHEMORADIOTHERAPY USING DYNAMIC SUSCEPTIBILITY-WEIGHTED CONTRAST-ENHANCED PERFUSION MR IMAGING WITH FERUMOXYTOL VS. GADOTERIDOL

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INTRODUCTION: Ferumoxytol as a blood pool agent offers reliable and simplified modeling of tumor blood volume assessment with no need of leakage correction methods application. Gadoteridol underestimates brain tumor blood volume measurements, likely due to extravasation artifacts, necessitating leakage correction to improve the accuracy of relative cerebral blood volume (rCBV) estimation. The purpose of this study is to compare rCBV measurement using gadoteridol versus ferumoxytol in glioblastoma multiforme (GBM) patients with progressive disease on conventional magnetic resonance imaging (MRI) after chemoradiotherapy and to correlate the rCBV with overall survival (OS). MATERIALS AND METHODS: Contrast leakage maps and rCBV were derived from dynamic susceptibility-weighted contrast-enhanced perfusion MRI which was performed using gadoteridol and ferumoxytol in 19 GBM patients when conventional MRI showed apparent tumor progression after chemoradiotherapy. Patients were classified as having high rCBV (>1.75) indicating tumor and low rCBV (≤ 1.75) indicating pseudoprogression for each contrast agent separately, and with or without contrast leakage correction for gadoteridol-rCBV. Statistical analysis used Kaplan-Meier survival plots with the log-rank test and Cox proportional hazards models. RESULTS: Ferumoxytol-rCBV was low in 9 (47%) patients with OS 591 days and high in 10 (53%) with OS 163 days, with hazard ratio 0.098 ($p = 0.0042$) indicating significantly improved survival. Gadoteridol-rCBV was low in 14 (74%) patients with OS 474 days and high in 5 (26%) with OS 156 days, with a non-significant hazard ratio of 0.339 ($p = 0.0928$). Five patients with mismatched high ferumoxytol-rCBV and low gadoteridol-rCBV had OS 171 days. After leakage correction application, the gadoteridol-rCBV hazard ratio was significant at 0.12 ($p = 0.0028$). CONCLUSION: Ferumoxytol as a blood pool agent facilitates differentiation between tumor progression and pseudoprogression and appears to be a good prognostic biomarker, and unlike gadoteridol does not require contrast leakage

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correction. Perfusion MRI using ferumoxytol in conjunction with conventional MRI will assist the clinician to avoid continuation of ineffective therapy and start second line or experimental therapy without delay in patients with active GBM after chemoradiotherapy as well as establish the patients with better prognosis who benefit from continuation of adjuvant temozolomide.

P.078. PREDICTIVE SIMULATION OF MRI AND FMISO-PET IMAGING CHANGES DURING ANTI-ANGIOGENIC THERAPY

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Despite extensive efforts in developing new therapies, median survival from glioblastoma remains about 14 months. While significant angiogenesis is a defining characteristic for high grade gliomas and a key mechanism by which tumor cells sustain and continue their aggressive growth, anti-angiogenic treatment remains controversial. We present the results of combining a bio-mathematical model of glioma growth and hypoxia with serial clinical imaging to quantify the effects of anti-angiogeneic treatment over a wide range of tumor kinetics. The model characterizes gliomas into distinct cellular phenotypes including normoxic, hypoxic, and necrotic cells that interact with each other and the microenvironment (vasculature). For a wide range of tumor growth and invasion kinetics, we simulated spatial maps of tumor cell density, hypoxia and edema under the affects of anti-angiogenic treatment and compared the results with clinically observed patient images. Simulated predictions were consistent with clinical observations on both anatomic MRI and 18F-fluoromisonidazole hypoxia PET imaging with transient stabilization or reduction of disease followed by progression. Simulations universally showed no significant changes in the tumor growth rates despite some changes in levels of edema and regions of hypoxia across virtual patients. This modeling approach provides a dynamic understanding of the biological connection between anatomical changes seen on MRI and biochemical activity seen on PET of gliomas in vivo while patients are undergoing anti-angiogenic treatment. In a patient-specific manner, the results quantitatively suggest that antiangiogenic therapies select for a more aggressive phenotype and changes on imaging can be sufficiently explained by the non-cytotoxic affects of the treatment on the vasculature, supporting their use as a surrogate for steroids.

P.079. FREQUENCY OF PSEUDOPROGRESSION IN PATIENTS WITH GLIOBLASTOMA ACCORDING TO RANO CRITERIA

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INTRODUCTION: It is reported that 20 -30 % of patients with high-grade glioma undergoing their first or second radiation MRI show increased contrast enhancement that subsides without any change in treatment. Because of this phenomenon, that is termed pseudoprogression, the recently introduced Response Assessment in Neuro-Oncology Criteria (RANO-criteria) suggest that within 12 weeks of completion of radiotherapy, progression can only be determined if the majority of the new enhancement is outside the radiation field. To validate this concept we assessed the frequency of pseudoprogression in a large cohorte of patients with glioblastoma at different time-points. MATERIAL AND METHODS: Patients with glioblastoma (n = 233) were examined between 1.1.2008- 12.31.2010. All patients received a baseline MRI after resection or biopsy of the glioblastoma, and further follow-up examinations every 3 months. All patients underwent standard radiotherapy with combined temozolomide subsequent to the operation. All patients who received external MRI or who received study-medication were excluded. Two experienced neuroradiologists (M.B. and A.R.) assessed if an enhancement-increase of at least 25% appeared within the radiation field at the follow-up examinations that qualifies for progressive disease (PD) at 3, 6, 9 and 12 months. In patients with MRI that demonstrated this progressive enhancement and hence progressive disease or pseudoprogression assessment of the evolution, over the next 6 months was done. Variables were increased or stable enhancement, enhancement that decreased less than 50%, more than 50 % or that disappeared completely. RESULTS: 158 Patients had to be excluded due to study participation (30), external MRI (70), no progression within one year (27) or insufficient MRI-examination (21). 85 Patients presented PD within the radiation field within one year after radiochemotherapy. Only 7,7 % of the patients presented increase of the enhancement three months after completion of radiochemotherapy that subsequently subsided. DISCUSSION: Our data challenge the introduced concept of pseudoprogression according to RANO-Criteria. We could not confirm the supposed value of 20 - 30% of pseudoprogression. However, an overestimation of pseudoprogression may result in a delay for the necessary change in therapy for the majority of patients who present real progression. To avoid these consequences frequency of pseudoprogression and other MR Imaging modalities such as perfusion-, diffusion or susceptibility-weighted imaging should be investigated for better sensitivity than T1/T2/FLAIR and a collaborative effort should be made on this topic in a multicenter study.

GLIOBLASTOMA AND ANAPLASTIC GLIOMAS

P.080. OUTCOMES FOR PATIENTS WITH HIGH GRADE GLIOMA TREATED WITH HYPO-FRACTIONATED RADIOTHERAPY AT UNIVERSITY HOSPITALS SOUTHAMPTON - A SINGLE CENTRE EXPERIENCE

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BACKGROUND: For patients with high grade glioma who are unlikely to tolerate long course chemo-radiotherapy, either due to advancing age or poor performance status, hypo-fractionated radiotherapy can be used to provide an optimal balance between efficacy and good palliation(1). METHODS: We performed a retrospective analysis of characteristics and outcomes for patients with high grade glioma receiving hypo-fractionated radiotherapy (30Gy in 6 fractions over 2 weeks, given on alternate working days), at our centre, over a three year period. RESULTS: Data was available for 49 patients. The median age was 70 (range 52-80). The majority (59%) had WHO performance status 2. Most patients (47%) underwent biopsy only, whilst surgical resection was undertaken for 39%. Diagnosis was confirmed by imaging criteria alone for the small remainder (due to adverse patient or technical factors). For those with a tissue diagnosis, the majority (80%) had glioblastoma multiforme. The median overall survival for patients was 19.5 weeks from diagnosis (95% CI 16.8-22.2). According to initial treatment (resection, biopsy only, radiology only) median survivals were 27, 16.5 and 15 weeks respectively. The median overall survival according to age (under/ over 70) was 19 and 19.5 weeks respectively. 31 patients had follow up imaging after radiotherapy. In 58% of patients, there was an initial radiological 'response', including stability. Subjectively, 57% of patients reported 'feeling better or the same' after radiotherapy. For 80% of patients, the dose of steroids was reported either as having been reduced or stable at review in clinic. No formal quality of life data was collected. CONCLUSION: The median survival for our patients treated with hypo-fractionated radiotherapy was 19.5 weeks which was similar to that of previously published data (2). Our retrospective analysis, with its limitations, does suggest that patients in this group, who underwent a surgical resection, are likely to benefit most from hypo-fractionated radiotherapy in terms of survival. Radiological stability was evident, at least initially for a significant group of patients. A significant proportion of patients were able to report either clinical stability or improvement, in addition to stabilising or reducing their steroid dose. The survival for patients who did not undergo surgical resection was markedly inferior. For this group in particular, the benefit or radiotherapy, when taken alongside its toxicities, is debatable. REFERENCES: 1: Radiotherapy Dose-Fraction (radiotherapy fractionation in the CNS). The Royal College of Radiologists, 2006. 2: McAleese, J.J et al. Hypo-fractionated radiotherapy for poor prognosis malignant glioma:-matched pair survival analysis with MRC controls. Radiother Oncol, 2003, 67:177-182.

P.081. FRACTIONATING VARIANTS FOR BRAIN TUMORS GRADE 3-4

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BACKGROUND: We analyse 438 patients with the verified tumors of a brain of high degree grade 3 (n = 112) or grade 4 (n = 326). METHODS: In Center clinic the classification allowing most effectively to prognosticate the general survival rate is developed and more accurately to define a regimen of a fractionating of radiotherapy at treatment of high degree gliomas. Adapted variant RTOG-RPA is based on major factors ($p < 0.01$): age, level of an Karnofsky Performance Status (KPS) and degrees (grade 3 or 4). For each of the listed factors the parametrical sizes reflecting their prognostic importance are entered. 1. *Age*: 0 - patients are younger than

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50 years; 1 - 50 years also are more senior. 2. *The functional condition*: 0 - KPS: 80-100 %; 1 - KPS: 60-70 %; 2 - KPS: 30-50 %. 3. *Degrees*: 1 - grade 3; 2 - grade 4. After introduction of the allocated parametrical sizes in a statistical database on each treated patient the prognostic class by a simple sum these parameters was defined. The statistical analysis was done with the SPSS 19.0 program. For studying of efficiency of model it was employing regression analysis of survival Cox. RESULTS: Five prognostic classes are allocated, authentic significance values for the general survival rate between classes. Probability of a lethal outcome in group of patients I - III classes by which the traditional of a fractionating (2 Gr) in 1,9 times more low (beta coefficient Exp(B)) in comparison by group, where used of 3 Gr ($p = 0.027$, 95% Cl: 1.077- 3.494), and in group IV - V ($p > 0.05$) differences of the general survival rate in a choice of a regimen of a fractionating it was not observed. At carrying out the regression analysis of survival Cox at classes IV - V the regimen (<>54 Gr at 2 Gr and <> 45 Gr at 3 Gr) has appeared the unique authentic factor for the general survival rate a dose-equivalent. Probability of a lethal outcome where the brought dose has appeared nonequivalent 54 Gr in 2 times above (beta coefficient Exp(B)) in comparison with doses-equivalent ($p = 0{,}006$, 95% Cl: 0,307-0,823). For classes I - IV besides fractionating regimens radicalism-dose authentically influences the general survival rate (60 Gr at 2 Gr and 51 Gr at 3 Gr) probability of a lethal outcome in group I - IV classes almost in 2 times above (beta coefficient Exp(B)) if the brought dose radical in comparison with not-radical regimen ($p = 0{,}000$, 95% Cl: 0,337- 0,655). CONCLUSION: Classifications RSCRR is effective for a choice of a regimen of treatment at high degree gliomas and can be recommended for use in practical neuroradiology.

P.082. PERMANENT EXPRESSION OF CHI3L1 GENE IS NECESSARY FOR SUPPORT OF MALIGNANT PHENOTYPE IN CHI3L1 TRANSFECTED 293 CELLS

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An important task in understanding oncogenesis is the identification of those genes whose copy number and expression increase during tumorigenesis. Among the genes with the pronounced increased expression in glioblastoma, the most aggressive form of brain tumors, was *CHI3L1*, encoding the secreted chitinase 3-like 1 protein. CHI3L1 can decrease the doubling time of 293 cells, allows the anchorage independent growth in soft agar and in addition, stable *CHI3L1* expression made 293 cells tumorigenic: these cells stimulated the initiation of tumors after their transplantation into the rat brains. 293_*CHI3L1* cells had activated extracellular signal-regulated kinases (ERK1/2)-mediated MAPK and AKT-mediated phosphoinositide 3-kinase (PI3K) pathways; phosphorylated ERK1 and ERK2 were localized in both cell cytoplasm and nuclei while AKT localized only in cytoplasm. 293_*CHI3L1* cells differed from 293 cells transfected by an "empty" vector in their size and ability to adhere to the culture plate. Thus, the overexpression of *CHI3L1* is likely to have an important role in tumorigenesis and orthotopic implantation of transformed human cells with overexpressed human oncogene *CHI3L1* to the rat brain presents a new model of human brain tumor which can be used as a target for anticancer drug development. It has been reported that *CHI3L1* expression positively correlated with high glioma grade and poor prognosis. To dissect the relationship between CHI3L1 and tumorigenesis, we employed a *CHI3L1* gene knockdown approach by siRNA transfection in 293 cells, which stably produced CHI3L1. Seventy two hours post-transfection, a noticeable protein blockade (80-90%) was obtained in 293 cells producing CHI3L1 with two different siRNAs to *CHI3L1* at concentrations ranged from 10 to 100 pM as compared with the control cells, which were transfected by control siRNA. It was confirmed by Western blotting in both 293_*CHI3L1* cells and U87MG cells. To identify further the influence of CHI3L1 on the intracellular signaling pathways, we then measured levels of pERK1 and pERK2. An active level of pERK1/2 was significantly reduced in 293 cells, which overexpressed *CHI3L1*, after transfection with siRNA_*CHI3L1* relatively to control cells. Despite reduction of *CHI3L1* expression in 293_*CHI3L1* cells we did not observe any morphological changes in these cells. CHI3L1 suppression 5,5-fold reduced the colony-forming ability of 293_*CHI3L1* cells after specific inhibition of CHI3L1 production as compared to control cells. Similar effect was obtained with glioblastoma U87 cells which expressed CHI3L1 on the RNA and protein levels. The obtained results demonstrate that activity of CHI3L1 mediated by pathways involved ERK1/2 and AKT has a growth-promoting role during tumorigenesis and indicate that efforts to inhibit its activity should be considered during cancer therapy.

P.083. PARAVENTRICULAR GLIOBLASTOMA AS DIFFERENTIAL DIAGNOSIS TO LYMPHOMA

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We present two cases of paraventricular glioblastoma in elderly male patients. Preoperative differential diagnosis included lymphoma. A 83 year old male patient complained of aphasia and hemiparesis for 3 weeks. In his past medical history there was prostate cancer. Open biopsy with neuronavigation confirmed the diagnosis of glioblastoma. Postoperative radiation and chemotherapy were performed and the patient died 6 months after initial diagnosis. A 78 year old male patient became symptomatic with recurrent syncopes. MRI revealed a paraventricular cystic contrast enhancing lesion. Microsurgical biopsy also with implantation of a Rickham reservoir was performed with neuronavigation. Neuropathological examination confirmed glioblastoma. Radio- and Chemotherapy were performed. The patient is neurologically in good condition 6 months after surgery. Paraventricular enhanced lesions are correlated with poor survival and histology is important in the differential diagnosis of these lesions so that navigated biopsy is recommended even in elderly patients.

P.084. EPITHELOID GLIOBLASTOMA WITH LEPTOMENINGEAL GLIOMATOSIS

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We present a 47 year old female patient who complained of neck pain and dizziness. On neurological examination an unsteady gait and memory disturbances were noted. MRI showed a contrast enhancing lesion in the left temporal lobe. No primary tumor was known. Whole body MRI showed no pathological findings. Intraoperatively the tumor was well defined and demarkated to the surrounding brain tissue. The tumor could be removed completely and the temporal horn of the ventricle was opened during tumor resection. The histological examination was quite difficult and the final diagnosis was epitheloid glioblastoma. EMA (Epithelial membrane antigen) was strong positive. This tumor is very rare and is mimicking metastasis. After radiation and chemotherapy our patient developed neck pain, meningism and confusion. MRI of her spine showed diffuse contrast enhancement of the dura. CSF examination confirmed tumor cells and leptomeningeal gliomatosis. She died 4 months after surgery.

P.085. THE ROLE OF CIRCULATING PROGENITOR CELLS IN BRAIN TUMORS

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OBJECTIVE: Blood circulating endothelial cells and circulating hematopoietic progenitor cells (CPCs) are two cell populations that are thought to play important role in angiogenesis. These cells populations are currently studied as surrogate markers mainly for heart disease and cancer. In the present study we examined the levels of CPCs in the peripheral blood of patients with gliomas and meningiomas. Furthermore, we investigated the relationship between the level of CPCs in the blood and the tumor's type, aggressiveness and patient's overall survival. MATERIAL AND METHODS: We prospectively studied nineteen patients who were operated on for brain tumors in our institute over a 2 year period. Ten controls free of brain tumor or pregnancy were also studied. Clinical variables that were analyzed included age, sex, Ki-67 index, tumor location, tumor size and preoperative Karnofsky performance status score (KPS). RESULTS: There were 11 males and 8 females (mean age 59.4 years, range 30 to 79). Twelve patients had a glioblastoma, 1 patient had a glioma grade II and 6 patients had a meningioma (four meningothelial and two transitional). Brain tumor patients had significant higher CPC levels compared to healthy volunteers. Patients with gliomas had significant higher CPC levels than patients with meningiomas ($p = 0.004$). No correlation was afound between CPC levels and sex, age, Ki-67 index, tumor location, size and KPS in glioblastoma. Patients with CPC levels lower than 1743 cells/ml had a higher progression-free survival but the difference was not statistical significant ($p = 0.18$). CONCLUSION: The present study demonstrated that CPC can be detected in the peripheral blood of patients with brain tumors. Glioma patients had significant higher CPC levels compared to patients with meningiomas. Larger studies are obviously needed in order to clarify the role of CPC levels monitoring in patients with brain tumors.

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P.086. INTERFERON-α/β ENHANCE TEMOZOLOMIDE ACTIVITY AGAINST MGMT-POSITIVE GLIOMA STEM-LIKE CELLS IN VITRO AND IN VIVO

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O6-methylguanine DNA methyltranferase (MGMT) is one of the main mechanisms of chemoresistance for alkylating agents in malignant gliomas. Recent studies have showed that glioma stem-like cells (GSCs) could be the main reason for tumor recurrence and chemoresistance. In this study, we aimed to explore the effects of interferon-α/β against MGMT-positive GSCs, and to investigate whether interferon-α/β can enhance the efficiency of temozolomide (TMZ) and the possible mechanism. The growth inhibition effect of TMZ, with interferon-α or interferon-β, against the MGMT-positive GSCs from human glioma cell lines U251 and SKMG-4 (U251G and SKMG-4G) was evaluated by using Cell Counting Kit-8 (CCK-8) assay in vitro, and in xenograft models. MGMT and NF-κB expression in the tumor samples were determined by RT-PCR and Western blot analysis. Our results revealed that the anti-tumor activity of TMZ was significantly enhanced by combined using interferon-α/β in vitro. In xenograft models, the tumor growth inhibit rate (IR) of TMZ to SKMG-4G and U251G was 35.2% ± 2.28% and 16.7% ± 1.96%, respectively. When TMZ combined with interferon-α or interferon-β, the IR to SKMG-4G was 58.4% ± 4.34% and 63.4% ± 1.08%; and to U251G was 41.1% ± 8.66% and 44.5% ± 1.90%, respectively($P < 0.05$).The expression of NF-κB and MGMT in MGMT-positive GSCs decreased significantly in both mRNA and protein levels after using interferon-α/β. Our results indicate that IFN-α/β can enhance the sensitivity of TMZ, possibly through down-regulate NF-κB expression resulting in lower MGMT transcription expression.

P.087. RE-IRRADIATION OF RECURRENT GLIOBLASTOMA MULTIFORME USING AMINO ACID PET IMAGE FOR HELICAL TOMOTHERAPY-BASED IMAGE GUIDED INTENSITY MODULATED RADIATION THERAPY

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PURPOSE: To develop a valid treatment strategy for recurrent glioblastoma multiforme (GBM) using helical tomotherapy (HT)-based image-guided intensity-modulated radiation therapy (IMRT) based on biologic imaging by ^{11}C-methionine positron emission tomography (MET-PET). MATERIALS/METHODS: The trial included a total of 17 patients with recurrent GBM after previous surgery and postoperative conventional radiotherapy chemotherapy. For fractionated stereotactic radiotherapy by HT-based IMRT treatment planning, the gross tumor volume (GTV) was defined by MET-PET/computed tomography (CT)/magnetic resonance imaging (MRI) fusion in all of the patients. GTV included the complete region of increased amino acid tracer uptake. The planning target volume (PTV) encompassed the GTV plus 3-mm margin. Treatment was performed with a total dose of 25-35 Gy, given as 5-7 Gy daily continually over 5 days. This dose was prescribed to the 95% isodose line, which covered the PTV. In 10 of 17 patients (59%), chemotherapy with temozolomide (TMZ) (150-200 mg/m^2 body surface/day) was continued after HT-based IMRT treatment. All patients were evaluated in follow-up by clinical investigators and MRI or MET-PET every 2 months after HT-based IMRT until death. RESULTS: The median tumor volume was 27.4 cm^3. With a median follow-up of 10 months, the overall survival time was 9 months from the date of HT-based IMRT treatment, with 6-month and 1- year survival rate of 64.7% and 20.2 %, respectively. The clinicoradiological progression-free survival time was 6 months from the date of HT-based IMRT treatment, with 6-month and 1- year survival rate of 52.9% and 17.6 %, respectively. Median survival time was 12 months for patients who received TMZ after HT-based IMRT and significantly lower, 5 months for patients without TMZ after HT-based IMRT ($p = 0.004$, log rank). The most important prognostic factor in univariate analysis was Karnofsky performance statuses (KPS) on the date of HT-based IMRT treatment ($p < 0.0001$, log-rank). In the multivariate model, KPS remained statistically significant ($p < 0.038$). No hematologic toxicity Grade 3 or higher was observed. Two patients experienced Grade 3/4 radiation necrosis, and necrotomy was required in one patient. CONCLUSION: This is the first study of biologic imaging optimized HT-based IMRT using MET-PET/CT/MRI image fusion in recurrent GBM. It demonstrates the feasibility and safety of this approach. Univariate analysis confirmed a significant survival benefit from multimodal treatment (i.e., addition of TMZ), despite the limited number of patients. Whether treatment planning with MET-PET independently influences survival has to be studied in a larger series of patients.

P.088. CEREBELLAR ANAPLASTIC ASTROCYTOMA IN A PATIENT WITH NEUROFIBROMATOSIS TYPE 1 - CASE REPORT AND REVIEW OF LITERATURE

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Low grade gliomas, e.g. pilocyticastrocytomas are frequently found in patients with neurofibromatosis type 1 (NF1). Whereas most of those lesions are located supratentorially, cerebellar manifestation is described in <1%. Moreover, malignant variants like glioblastoma and anaplastic astrocytoma are only rarely observed in both cerebellar and cerebral tumors in NF1-patients. We present the case of a 54 years old male patient with von Recklinghausen's disease suffering from cerebellar diffuse contrast enhancing mass which was treated by fluorescence guided resection. Histopathological analyses revealed an anaplastic astrocytoma with lack of pilocytic features and adjuvant temozolomide chemotherapy was administered. Follow up was achieved for sixteen months. Although the patient recovered quickly after the operation and tumor progression was ruled out in follow up MRIs, the patient impressively deteriorated cognitively and MRI revealed a severe leucoencephalopathy. Although extended neurological examination was performed, etiology of the leucoencephalopathy still remained unknown at the date of manuscript submission. We additionally reviewed the literature and summarized and discussed two previously published case reports. Tumor control after resection was achieved in all three patients; however, the patients in the previous reports received either radiation or combined radiation and chemotherapy instead of chemotherapy alone.

P.089. PHASE II STUDY OF IFOSFAMIDE, CARBOPLATIN, AND ETOPOSIDE IN PATIENTS WITH A FIRST RECURRENCE OF GLIOBLASTOMA

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OBJECT: 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 life. METHODS: This trial was an open-label, single-center Phase II study. Forty-two patients with a first GBM relapse after surgery followed by standard radiotherapy (60 Gy) and first-line temozolomide- or nimustine-based chemotherapy were eligible to participate. The primary end point was progression-free survival at 6 months after the ICE treatment (PFS-6), and secondary end points were response rate, toxicity, and overall survival. Chemotherapy consisted of ifosfamide (1000 mg/m2 on Days 1, 2, and 3), carboplatin (110 mg/m2 on Day 1), etoposide (100 mg/m2 on Days 1, 2, and 3), every 6 weeks. RESULTS: Progression-free survival at 6 months after ICE treatment was 35% (95% CI 22-50%). The median duration of PFS was 17 weeks (95% CI 10-24 weeks). The response rate was 25% (95% CI 9-34%). Adverse events were generally mild and consisted mainly of alopecia. CONCLUSIONS: This regimen was well tolerated and has some activity and could be one of the options for patients. with recurrent GBM.

P.090. TREATMENT RESULTS OF GAMMA KNIFE RADIOSURGERY FOR RECURRENT MALIGNANT GLIOMA

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PURPOSE: Ultimately despite this current standard treatment, almost all patients with malignant glioma will have relapse. Gamma knife radiosurgery (GK) is a relative safe and less invasive treatment used as adjuvant therapy for patients with recurrent malignant glioma. This study is a retrospective review of our institutional experience with GK adjuvant therapy in the treatment of recurrent malignant glioma. METHOD: Between 2006 and 2011, 41 patients with recurrent malignant glioma (13 anaplastic astrocytoma: Grade III, 28 glioblastoma: Grade IV) were treated with GK in Nakamura Memorial Hospital. GK was performed at the time of recurrence after early stage treatment. One hundred-nine lesions were treated with GK. As

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first-line radiotherapy, fractionated external beam radiotherapy (54-60Gy) was performed in all patients before GK. Chemotherapy based temozolomide was administered to the extent feasible. The median interval between initial diagnosis and primary GK was 13.5 months (range, 2-98 mos). The median target tumor size was 11.0 cm^3 (range, 0.1-54.7 cm^3). The median marginal doses were 17Gy (range 10-20Gy), and the median maximal doses were 33Gy (range 21-40Gy), prescribed to the 53% (range 40-95%) isodose line that encompassed the target volume. The median follow-up time was 24.3 months (range 3-137mos). Progression-free survival (PFS) and overall survival (OS) were performed using the Kaplan-Meier actuarial method. RESULT: The median OS from the time of diagnosis was 23 months for Grade III and 21 months for Grade IV. One- and two-years survival rates from the time of diagnosis were 82% and 45% for Grade III and were 89% and 45% for Grade IV. PFS from the time of GK was 3 months for Grade III and Grade IV. The 6-month PFS from the time of GK was 28% for Grade III and was 18% for Grade IV. The median OS from the time of GK was 11 months for Grade III and Grade IV. Stratification by RPA criteria showed 10, and 21 patients, respectively, in class 3 and 7. Median OS for our patients compared to the NABTC database was as follows: 7.0 months vs. 3.8 months for class 3; 10.0 months vs. 4.9 months for class 7. CONCLUSION: GK showed a survival benefit in RPA classes of the NABTC databases for class 3 and 7. GK was comparable to treatment result of second-line chemotherapy as adjuvant treatment. GK is a relative safe and less invasive treatment and may play an important role in the treatment of recurrent malignant glioma.

P.091. ABTC 0906: A PHASE II AND PHARMACODYNAMIC TRIAL OF RO4929097 FOR PATIENTS WITH RECURRENT/ PROGRESSIVE GLIOBLASTOMA

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INTRODUCTION: Cancer stem-like cells (CSCs) are capable of self renewal and differentiation within a tumor. These properties are likely a major cause of resistance to chemotherapy and radiotherapy. Therefore, CSCs are an attractive target for therapy of GBM. Proliferation of CSCs occurs via several signaling pathways. One of the major pathways is Notch. Expression of Notch is critical for survival and proliferation of human gliomas. Gamma secretase (GS) is a critical enzyme in the Notch pathway. Therefore, disruption of the Notch pathway by inhibition of GS is a logical treatment strategy for patients with GBM. RO4929097 is an oral small molecule inhibitor of GS. This phase II and pharmacodynamic study assesses the efficacy of RO4929097 against recurrent GBM (rGBM) and includes biomarker assays on freshly resected GBM samples from patients receiving this agent. METHODS: Two groups of adults with contrast-enhancing rGBMs are eligible: Group A - 40 patients who receive RO4929097 only, and Group B - 20 patients who receive drug before and after resection of rGBM. Although prior GS inhibitors are excluded, the trial allows an unlimited number of prior chemotherapy regimens as well as bevacizumab. The primary endpoint is PFS_6. Secondary endpoints include biomarker studies on fresh tumor from Group B patients. Tumor tissue is assayed for neurosphere generation; expression of Notch pathway components and downstream targets; and survival of mice bearing orthotopic xenografts. A 25% reduction of neurosphere generation compared to a contemporaneous group of rGBM patients will be considered significant. In group B patients, pre- and post-operative plasma pharmacokinetics are obtained. The concentration of RO4929097 is determined by high performance liquid chromatography with electrospray ionization mass spectrometric detection. RESULTS: To date 38 patients in Group A and 7 in Group B have enrolled. Group A patients had median age 58 (range 35-75), median KPS 80 (range 60-90), and 66% were male. Twenty-five of 38 Group A patients had complete progression data and 13 are still too early to evaluate. With this incomplete follow up, the median PFS_6 is 1.7 months (range: 0.7 -3.2). Correlative biology and updated clinical data are pending. CONCLUSIONS: This study is designed to provide preliminary information on drug effect in patients (Group A) and in tumor samples resected from patients and studied in neurospheres and implanted in mice (Group B). Mature results of outcomes and pharmacodynamic analyses will be presented at the meeting. (Funded by NIH U01 CA 137433).

P.092. TELOMERASE-ASSOCIATED PARAMETERS: PROGNOSTIC MARKERS FOR GLIOBLASTOMAS?

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Patients with glioblastomas (GBM) have variable clinical courses, but the mechanisms that underlie this heterogeneity are not clarified yet. In search of prognostic biomarkers we focussed on telomerase activity (TA), the catalytic subunit human telomerase reverse transcriptase (hTERT) and length of telomeres (TL). The enzyme telomerase, reactivated in most cancer cells maintains telomere length by adding a six-base motif (TTAGGG) to the telomeric ends of chromosomes thus promoting cell immortalization and oncogenesis. In the present study we investigated GBM tumor tissue from patients ($n = 100$) operated at our institution. Telomerase activity (TA), hTERT expression and length of telomeres (TL) were analysed using the Telomeric Repeat Amplification Protocol (TRAP), RT-PCR and quantitative PCR, respectively. Additionally these parameters were correlated with disease progression. Sixty-one percent of GBMs were positive for both hTERT and telomerase activity. Despite of inconsistency in 2 cases (hTERT negative/ TA positive) the correlation between hTERT and TA was highly significant (Fisher's exact test, $P < 0.0001$). Measurement of telomere length revealed a statistically significant difference between the hTERT/TA positive and negative subgroups showing markedly longer telomeres in the hTERT/TA negative cohort (unpaired t test; $p = 0.0001$). Additionally, similar results were achieved by comparing age grouped ($>< 60y$) patients (unpaired t test; $p < 0.0001$). Statistical analyses (χ^2 test) of telomere-related parameters and patient characteristics revealed significant correlations between age and both hTERT expression and TL ($p < 0.05$), while the one for TA reached only borderline significance ($p = 0.059$). Additionally, a worse KPS was associated with both hTERT expression and higher TA significantly ($p < 0.003$), whereas only a trend towards shorter TL was observed (p 0.09). Accordingly, those patients eligible for any treatment subsequent to surgery harbored significantly lower hTERT expression (p 0.04) and a tendency towards reduced TA (p 0.067). Mutations in IDH1 were distinctly linked to telomerase negativity and enhanced telomere lengths. No significant association was observed between telomerase-related parameters and MGMT promoter methylation. Moreover, analysis of Kaplan Meier survival estimates revealed a significant survival benefit for patients whose tumors lack either hTERT expression ($p < 0.005$) or TA ($p = 0.0008$) preferentially in a subgroup of patients of younger age. In summary, these data suggest that GBMs showing reactivated telomerase provoke a more aggressive clinical type of tumor reflected by significantly shorter telomeres and associated with significantly shorter overall survival. Thus, hTERT and telomerase activity might have quality as prognostic biomarker especially in the subgroup of patients of younger age.

P.093. EXPRESSION OF MULTIDRUG RESISTANT GENES IN THE HUMAN GLIOBLASTOMAS

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BACKGROUND: Glioblastomas are frequently chemoresistant and this resistance seems to depend on many mechanisms. One of these problems is overexpression of multidrug resistant genes in the blood brain barrier (BBB) and the glioblastoma cells themselves. This BBB forms a very effective barrier to the free diffusion of many polar solutes into the brain. Many metabolites that are polar have their brain entry facilitated by specific inwardly-directed transport mechanisms. These molecules are substrated for the ABC (ATP-binding cassette) transporter proteins which are present in BBB, and the activity of these transporters very efficiently removes the drug from CNS, thus limiting the brain uptake. In addition, the malignant gliomas are highly vascularized tumor. In the process of vasculogenesis, de novo formation of blood vessels from bone marrow-derived endothelial progenitor cells (EPCs) takes place. The two surface markers CD133 and VEGFR characterize the primitive EPCs. We hypothesized that patients with the malignant gliomas have increased levels of EPCs, and the increased EPCs and amplified ABC transporter proteins reportedly play roles in the cancer chemotherapy problems. MATERIALS & METHODS: In the present study, we investigate that the multidrug resistant genes (MDR1, MRP1-5, ABCG2, MGMT and Topoisomerase II), CD133, VEGFR1 and 2 and EGFR in 24 human glioblastomas specimens using RT-PCR assay and immunohistochemical staining. RESULTS: We demonstrated the presence of ABC transporter proteins in the microvessel endothelium of human malignant gliomas. Furthermore, we observed overexpression of CD133, VEGFR1 and VEGFR2 in glioblastoma with MDR1, ABCG2 and MGMT amplification. Glioblastomas with MDR1, ABCG2, MGMT, CD133, VEGFR1 and VEGFR2 amplification tend to have a tendency of a shorter median progression free survival. MDR1, MRP1, ABCG2, MGMT CD 133, VEGFR1 and VEGFR2 are amplified in the recurrence of glioblastoma.

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CONCLUSIONS: The increased EPCs and amplified ABC transporter proteins probably resist the cancer chemotherapy with consequent poor outcomes in glioblastomas. Measuring the expression of the drug-resistant genes, CD133 and VEGFR can be useful for the management of glioblastomas.

P.094. OBSERVATION OF THE FREQUENCY OF MGMT METHYLATION, BRAF V600E MUTATION AND IDH1/2 MUTATIONS IN A GREEK BRAIN TUMOR COHORT

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In the past few years, extensive molecular studies have identified diagnostic and prognostic markers in Gliomas. 1p19q co-deletion, O(6)-methylguanine DNA methyltransferase (MGMT) status, and mutations of isocitrate dehydrogenases 1 and 2 (IDH1/IDH2) are currently the three most pertinent markers in diffuse gliomas. The RAS/RAF (MAPK) signalling pathway is one of the most prominent pathways for regulation, cell growth, proliferation, differentiation and apoptosis in malignant cells. The role of aberrant activation of RAS signalling in gliomas pathogenesis is not clear at this time. BRAF, an immediate downstream target of the Ras protein has been identified as a frequent target of activating mutations in gliomas. Recently, genomic aberrations of the B-RAF oncogene have been described in adult malignant gliomas, however the clinical and prognostic significance of BRAF mutation for overall survival has yet to be established. The purpose of this study was to evaluate a possible correlation between MGMT status, IDH1 and BRAF mutations and the clinicopathological features as well as prognosis in Malignant Gliomas patients. We collected tissue samples of primary tumor biopsies from 31 adult patients with histologically proven malignant gliomas. Of 31 patients, 80,5% had Glioblastoma Multiforme, 6,5% Anaplastic Astrocytoma grade III and 6,5% Oligodendrioglioma grade III and 6,5% Anaplastic Astrocytoma with Glioblastoma Multiforme. DNA was extracted from Formalin-Fixed Paraffin Embedded (FFPE) tissue using the Qiagen QIAmp DNA FFPE® tissue kit. Selective PCR amplification was carried out using specific primers for the *BRAF* gene. The methylation pattern in the CpG island of *MGMT* was determined by chemical modification of unmethylated, but not methylated, cytosines to uracil, using the EpiTect Bisulfite Kit (Qiagen). Exon 4 of the IDH1 genes was amplified by Polymerase chain reaction. Mutation detection was carried out by sequencing analysis. Among our patient population, 84% had MGMT methylation, 10% carried IDH1 mutations, and 6% had a BRAF V600E mutation. All of the IDH1 mutant patients had a lower grade disease (Anaplastic Astrocytoma Grade III and Oligoderdroglioma Grade III) in accordance with the literature, while BRAF V600E mutations were assosiated with with a more agressive disease. Of the MGMT methylated patients with GBM, 10% had the V600E mutation on BRAF and none had a mutation on IDH1 or 2. From our research we concluded that the use of molecular markers along with clinicopathological parameters can be a helpful in determining the prognosis of patients with brain tumors. There is a definite need for a larger scale analysis of these markers in a bigger patient cohort.

P.095. LASERSPECTROSCOPY IN 5-ALA TREATED GLIOMAS: SPECTROSCOPICAL EVALUATION OF 5-ALA FLUORESCENCE UPTAKE AND KINETICS IN HUMAN GLIOMA CELLS

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INTRODUCTION: 5-aminolaevulinic acid (5-ALA) has improved surgical therapy of malignant gliomas. However, there is a lack of knowledge concerning 5-ALA uptake and fluorescence kinetic in different histologies. Aim of this study was to detect differences in malignant gliomas concerning uptake kinetic and fluorescence of 5-ALA loaded glioma cells by spectroscopy. METHODS: Sample examination took place 4 hours after 5-ALA application. Before surgery, 20 mg /Kg bodyweight 5-ALA was given. Tumor slices which showed a maximum of fluorescence using the surgical microscope at the beginning and during resection, were cut into 1cm3 blocks, incubated in 5% glucose solution and used for spectroscopical evaluation by an un-pulsed diode laser with a wavelength of 405 nm and with an energy of 30 mW combined with a spectroscope. The distance between laser and example was 1 mm. Measurements were performed every hour for 1 second in order to reduce a photo bleaching effect starting at baseline 4 hours after 5-ALA application and ending 14 hours after 5-ALA application. RESULTS: The tumors of 8 patients were evaluated of which 5 were glioblastomas (GBM) and 3 anaplastic astrocytomas (AA). We observed a reduction in fluorescence accumulation in the cells in a negative exponential way. A photo bleaching effect was detected in slices, analyzed for more than 1 second. AA showed significantly lower 5-ALA-uptake as well as a significantly lower curve in total fluorescence compared to GBM. CONCLUSION: In gliomas, 5-ALA fluorescence decreases in a negative exponential curve helping to interpret the kinetics and intraoperative findings. This observation may be useful for intraoperative predictions of histology.

P.096. A RANDOMISED PHASE II STUDY OF CARBOPLATIN AND BEVACIZUMAB IN RECURRENT GLIOBLASTOMA MULTIFORME (CABARET STUDY)

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BACKGROUND: Glioblastoma (GBM) is the most aggressive malignant glial tumor, and eventual progression is almost universal. There is no accepted standard management after disease progression. The combination of carboplatin and bevacizumab for recurrent GBM has not been studied prospectively. Much remains unknown about the optimal use of bevacizumab, including the role of continuing beyond radiological progression, and patterns of progression during and after bevacizumab use. In addition, the new Response Assessment in Neuro-Oncology (RANO) criteria have yet to be validated prospectively. METHODS: The CABARET clinical trial is a multi-centre, sequential stratified randomised phase II study. Patients have recurrent GBM after radiotherapy and temozolomide, have had no other chemotherapy for GBM, have ECOG performance status 0-2, and measurable disease or resected recurrence. At least three months must have elapsed since radiotherapy. In Part 1, patients are randomized 1:1 to intravenous bevacizumab 10 mg/kg 2-weekly and carboplatin AUC5 4-weekly or to bevacizumab monotherapy. In Part 2, on progression, patients suitable to continue treatment are randomised to continue or cease bev. The primary objective is to determine the effect of bevacizumab plus carboplatin versus bevacizumab alone on progression-free survival (PFS) according to modified RANO criteria. Secondary endpoints are response rates (both modified RANO and modified MacDonald criteria), cognitive function, quality of life, steroid dose, toxicity, and overall survival. CogState, a validated neurocognitive testing system, is being used prospectively for the first time in a brain tumor trial and compared with mini-mental state examination. Exploratory endpoints include biomarker analyses, comparison of modified RANO and modified MacDonald criteria, predictive value of early MRI following 2 doses of bevacizumab, steroid dosing, and location and type of radiological progression during and after bevacizumab therapy. Patients are stratified by centre, age, sex, and performance status. RESULTS: This study commenced enrolment in Nov 2010, completing accrual to part 1 in Mar 2012 with 122 patients randomised from 18 Australian sites. Randomisation to Part 2 is ongoing. Feasibility and safety data will be presented; efficacy outcome results are not anticipated until 2013. The study results will significantly improve knowledge regarding the use of bevacizumab in the setting of recurrent GBM, as well as providing for the first time a prospective analysis of the CogState neurocognitive testing system for patients with brain tumours.

P.097. REDUCTION AND DELAY OF TUMOR GROWTH BY ACTIVATING MACROPHAGES - STIMULATION OF THE INNATE IMMUNE RESPONSE IN ORTHOTOPIC RODENT GLIOMA MODEL BY APPLICATION OF RHGM-CSF

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OBJECTIVE: The host immune response plays a pivotal role in tumor progression. To date, cytotoxic CD8+ T-cells and NK cells have been considered the main cellular components of host tumor control. We studied the influence of macrophages in the orthotopic C6 tumor implantation model and previously discovered a pronounced increase of tumor growth when macrophages were depleted with clodronate. Here we describe the tumor progression pattern when macrophages are activated using granulozyte macrophage colony stimulating factor (rhGM-CSF, Leucomax). METHODS: 20 Sprague-Dawley rats carrying orthotopically implanted C6 glioma spheroids were treated with s.c. 10 µg/kg rhGSM-CSF. 12 animals served as controls. Serial MRI-Scans (T1, T2 and 3D CISS-Sequences) were performed on days

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7, 14, 21, 28, 32 and 42 post-implantation. Tumor-volumes were determined by MRI. Histological work-up included HE, CD68/ED-1 macrophage, CD8 T-cell, and Ki-67 MIB1 proliferation staining in brain, tumor and spleen. RESULTS: Tumors developed in 13 of 20 animals. On day 7 none of the animals showed tumor-growth on MRI. Solid tumors were seen in 9 of 15 (60%) animals on day 14 which is in contrast to control animals where tumor growth was seen on MRI in 10 of 12 animals (83%). 3 of remaining 13 animals first showed solid tumor on day 21. Tumors developed significantly later and remained smaller with a median size of 134 mm^3 in the GM-CSF series compared to controls with 150 mm^3. Immunohistochemistry was used to count macrophages in the implanted tumors as well as corresponding spleens which were used as control tissue to confirm the effect of GM-CSF stimulation. CONCLUSION: Stimulation of macrophages by GM-CSF leads to significantly reduced and delayed tumor growth in the rodent C6 glioma model. The presented data underline the significant role of the innate immune response by macrophages in host control of experimental gliomas. Modulating macrophage activation had a marked effect on tumor growth, whereas T-cell depletion had little or no effect. Macrophages have been underrated in host tumor control.

P.098. MOLECULAR, PHENOTYPIC, AND FUNCTIONAL CORRELATES OF ALTERNATIVE LENGTHENING OF TELOMERES (ALT) IN HIGH GRADE ASTROCYTOMAS

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BACKGROUND: The telomerase-independent mechanism of telomere maintenance known as Alternative Lengthening of Telomeres (ALT) is known to occur in subsets of human cancers, and recent studies have demonstrated a. strong association with *ATRX* mutations in human gliomas. We retrospectively reviewed human glioblastomas (GBM) and anaplastic astrocytomas (AA) to uncover correlations between ALT, ATRX expression, histology and molecular alterations typical of infiltrating. astrocytomas. METHODS: We studied 117 high grade astrocytomas with available ALT status (34 pediatric GBM, 64 adult GBM, 18 adult AA, 1 pediatric AA). Histologic evaluation was performed in whole H&E sections in most cases ($n = 93$). Molecular and immunohistochemical studies were performed on tissue microarrays. Immunohistochemistry was performed using antibodies against ATRX, DAXX, and IDH1R132H mutant protein. *EGFR* amplification was evaluated by fluorescence in situ hybridization (FISH). RESULTS: ALT was identified in 40 cases (34%), including 17 (89%) grade III astrocytomas, and 23 (24%) grade IV astrocytomas, as previously reported. When focusing on histologic subtypes, almost half of fibrillary and gemistocytic astrocytomas (41%) were ALT positive. Conversely all gliosarcomas ($n = 4$), epithelioid ($n = 2$), giant cell ($n = 2$) and adult small cell astrocytomas ($n = 7$) were ALT negative. The ALT phenotype was positively correlated with the presence of round cells ($p = 0.002$), microcysts($p < 0.0002$), IDH1 mutant protein ($p < 0.0001$), ATRX protein loss ($p < 0.0001$), and absence of *EGFR* amplification ($p = 0.004$). There was no significant correlation with DAXX expression. Patients with ALT positive tumors also demonstrated an increased overall survival compared with ALT negative tumors ($p = 0.004$) by univariate analysis. We have identified an ALT positive neurosphere line (JHH-GBM14) which also demonstrates ALT in the primary GBM from which it was derived. We have also examined two pediatric GBM cell lines (JHH DIPG and SU-DIPG) that lack ALT and express ATRX. Functional *in vitro* studies using these lines, and screens for additional lines, are in progress in our laboratory. CONCLUSION: ALT represents a specific phenotype in high grade astrocytomas with distinctive pathologic and molecular features. Further studies are required to clarify the clinical and biological significance of ALT in high grade astrocytomas.

P.099. PRIMARY MALIGNANT BRAIN TUMORS IN THE ELDERLY: RETROSPECTIVE ANALYSIS OF MANAGEMENT AND OUTCOME

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INTRODUCTION: Increasing life expectancy has led to a rising incidence of primary malignant brain tumors in the elderly. Optimal management in this population is uncertain because of lack of reliable outcome data from relevant trials, age-related factors such as comorbidity, therapy tolerance and toxicity and diminished therapeutic effect due to an increase in genetic aberrations. The discussion is also influenced by ethical and economic arguments. METHODS: We retrospectively analyzed our database of all patients aged ≥70 admitted to the neurosurgery department between 2004 and 2012 with a diagnosis of a primary malignant brain tumor. We assessed age, Karnofsky performance score (KPS), histology, treatment, progression-free survival (PFS) and overall survival (OS). A total of 86 patients were included. Differences between groups were tested for significance using Mann-Whitney U test. RESULTS: Mean age was 75 years (SD 3,7), 37 were female (43%) and 49 male (57%). Median PFS and OS were 102 days and 165 days respectively. In 67 patients (77,9%) tissue diagnosis was obtained: 59 glioblastomas, 7 anaplastic astrocytomas and 1 grade III ependymoma. 58 (87%) received active therapy. In 19 patients no tissue diagnosis was obtained: in 2 biopsy was inconclusive, in 17 no biopsy was taken and MRI diagnosis was deemed sufficient. These patients were on average older and in worse condition (median age 78 years, median KPS 60).Only 5 patients in this group were given active treatment. In total, 63 patients (73,3%) received active treatment, with a median KPS of 70, median PFS of 149 days and median OS of 189 days. Treatment consisted of gross-total resection in 37 patients, radiotherapy (RT) in 55, chemotherapy in 39. Five patients were included in a dendritic cell vaccination (DCV) trial. In this way, combination of temozolomide (TMZ) and RT was administered to 32 patients of whom 21 patients also were operated. The 5 patients in whom active therapy was given without histology received radiotherapy. Thirteen patients were given additional therapy (resection and/or chemotherapy) after progression, with a median PFS of 328 days and median OS of 498 days. 23 patients, with a median KPS of 60 (range 30 - 90) received only supportive care, with median OS of 68 days. A significant difference in KPS and OS was found between the active treatment group and the supportive care group ($p <$ 0,001). 15 patients (17,4%) were above 80 years, of whom 8 received active treatment. These had a median KPS of 85 and a median OS of 146 days compared to a median KPS of 60 and median OS of 125 days in the supportive care group. CONCLUSION: Active treatment for elderly patients with malignant glioma can be worthwhile esp. under 80 years. Age alone is insufficient to exclude patients from treatment. Further studies assessing biological rather than calendar age as determinant for treatment are needed.

P.100. COMPASSIONATE, OFF-LABEL USE OF SINGLE-AGENT BEVACIZUMAB IN PATIENTS WITH RECURRENT GLIOBLASTOMA

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BACKGROUND: The management of patients (pts) with recurrent glioblastoma (GBM) after Radiotherapy (RT) plus Temozolomide (TMZ) remains undefined and has dismal prognosis. Antiangiogenic monoclonal antibody Bevacizumab (BEV) has shown significant antiglioma activity with promising response rates and some quality of life improvement in both retrospective and prospective phase II studies. PURPOSE: To test the feasibility and clinical benefit of BEV in off-trial, unselected pts with progressive disease after surgery and Stupp-based treatment protocols. PATIENTS AND METHODS: From the period 04/2009 to 12/2011, eight consecutive pts with recurrent/progressive GBM were administered with single-agent BEV 10 mg/kg every 2 weeks. Median age of pts was 44 (range 34-67), male/female ratio 4/4, median Karnofsky Performance Status 70 (60-90). No limits on the number of previous progressions/treatments were allowed: all pts had been treated with RT + TMZ, three had TMZ altered schedules for re-challenge, one received fotemustine. Magnetic resonance evaluations were repeated every 4 cycles of BEV. RESULTS: Median number of administered cycles was 5 (3-11). Five partial remissions, two stable diseases and one progressive disease were achieved. Median progression-free survival was 14 weeks (4-42), median overall survival was 31 weeks (20-44). No serious adverse events such as thromboembolism, hemorrhage, bowel perforation occurred. Mild hypertension was only detected in 2 pts as drug-related immediate toxicity. Responders experienced significant regression of neurological symptoms and some quality of life improvement (Barthel Index, SF36QoL questionnaire). CONCLUSIONS: Despite the heterogeneity of pts and some heavy previous treatments, the current experience confirms that BEV monotherapy has interesting clinical activity in recurrent GBM and a good acute toxicity profile even in off-trial, unselected pts.

P.101. SIDE POPULATION IN HUMAN GLIOBLASTOMA DOES NOT CHARACTERIZE CANCER STEM CELL POPULATIONS AND IS EXCLUSIVELY STROMA-DERIVED

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Progression of glioblastoma is proposed to be triggered by a cancer stem cell population, postulated to be responsible for tumor recurrence due to their resistance to radio- and chemotherapy. Resistance mechanisms may involve ATP-binding cassette (ABC) transporters on the cell membrane, which are responsible for drug efflux from the cell and may therefore represent putative cancer stem cell (CSC) markers. We investigated the presence of the Side Population (SP) phenotype, which is recognized by increased efflux of the Hoechst dye through ABC transporters, in human glioma biopsies as well as in intra-cranial xenograft models derived from human biopsy spheroids and stem-like glioma cultures. We used a GFP expressing immunodeficient mouse model, enabling to separate tumor cells from host stromal cells, thereby allowing to clearly identify the cellular origin of the SP cells. Interestingly we find that SP cells in human gliomas is uniquely stroma-derived, thus indicating that the SP phenotype is not a valid marker for glioma CSCs. Indeed the SP population present in glioma tissue is composed of endothelial and astrocytic cells, whereas neither stromal nor tumor-derived stem/progenitor populations in the adult brain possess efflux properties. We further determined the effect of anti-angiogenic treatment by bevacizumab on the efflux properties of stroma-derived endothelial cells in order to address the question whether normalization of the vasculature induced by anti-VEGF agents constitutes an advantage or an impediment for drug delivery in the brain. The results on stromal-derived as well as tumor-derived endothelial cells will be discussed.

P.102. TEGWONDO-CCNU - A NOVEL COMBINATION OF PROTRACTED, NEAR-CONTINUOUS TEMOZOLOMIDE AND CCNU WITH ACTIVITY IN RECURRENT MALIGNANT GLIOMAS

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BACKGROUND: alkylating chemotherapy with CCNU is active in recurrent 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: 25 consecutive patients with recurrent malignant gliomas (12 anaplastic gliomas WHO III, 13 glioblastomas and gliosarkomas WHO IV) were treated: 15 males (60%), 10 females (40%); mean age at start of chemotherapy was 52 (20-78) years; Eight patients were treated for a first, 15 for second and two for third recurrence. All patients were pretreated with temozolomide. Four patients received a second irradiation (FSRT) in parallel. Nine of the 11 patients were switched without delay from dose-dense temozolomide monotherapy to combined near-continuous temozolomide (50-60mg/m2 day 1 5/7) plus weekly low-dose CCNU (40mg fix dose at day 6/7). RESULTS: in total, 89 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 $3 + 4$ toxicity occurred in 5/25 patients (20%), two of them were symptomatic. Three patients had a prolonged elevation of liver enzymes. Best responses after ≥ 3 months (23 patients) were: 2 complete and 1 partial remissions (13%), 13 stable diseases (57%), and 7 progressive diseases (30%). Median overall survival after start of chemotherapy for the 16 patients treated > 6 months or dead was 6.3 months, progression-free survival at six months (PFS 6) 37%. 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 conventionally dosed or dose-dense temozolomide alone. Hematotoxicity, though, has to be controlled vigorously. The results have to be controlled in a larger, prospective series.

P.103. SUBVENTRICULAR ZONE INVOLVEMENT DOES NOT PREDICT ADVERSE OUTCOMES IN GLIOBLASTOMAS

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BACKGROUND: Recently it has been shown that glioblastomas (GBM) arising in close proximity to periventricular regions have an aggressive behaviour and may confer an adverse outcome. Its implications on survival however remain unclear MATERIALS AND METHODS: Eighty-four patients with GBMs were analysed. Radiology was reviewed in all patients and tumor relationship to subventricular zone (SVZ) recorded. Routine clinical, surgical, and treatment details were recorded. Progression free and overall survivals were calculated. Univariate and multivariate analysis was done to assses the role of known prognostic markers (age, KPS, RPA class, extent of resection) as well as mltifocality and relation of the tumor to the SVZ areas. RESULTS: Radiological (MRI) evaluation revealed involvement of SVZ in 54 (64.3%). Multifocality at presentation was present in 19 cases (22.6%) [15 of the SVZ group ($p = 0.176$)]. Gross total excision was achieved in 93.3% of those with no SVZ involvement versus 61% of those with SVZ involvement ($p = 0.02$). 57 patients completed radiotherapy with or without concurrent and adjuvant temozolomide. MR at progression was available in 31 (20 of the SVZ group). Distant relapse occurred in 8 cases (5 of these being in the SVZ group, $p = 0.42$). Median PFS and OAS were 9 and 9.8 months respectively. Univariate analysis yielded only RPA class, completion of radiotherpay and chemotherapy to be prognostically significant for OAS and PFS, the latter two being significant on multivariate analysis too. SVZ involvement was not statistically significant, though it showed a strong trend for decreased survival. CONCLUSION: Involvement of the SVZ by itself may not be a poor prognostic marker in patients with glioblastomas. It however may preclude radical resection which may adversely impact the outcome.

P.104. RE-IRRADIATION WITH OR WITHOUT TEMOZOLOMIDE IN PATIENTS WITH RECURRENT GLIOMA PROLONGS MEDIAN SURVIVAL WITH LOW TOXICITY

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PURPOSE: to determine the overall survival (OS) and progression free survival (PFS) after re-irradiation for recurrent glioma and establish the prognostic factors that determine OS and PFS after re-irradiation. MATERIALS/METHODS: Sixty-six patients received re-irradiation (Re-RT) for a recurrent glioma at MAASTROclinic between January 2003 and September 2011. 74.2% of patients presented with a glioblastoma (GB) at recurrence (primary $n = 35$, secondary $n = 14$). Conformal radiotherapy, stereotactic radiotherapy and intensity modulated radiotherapy treatment techniques were used. Re-RT was preceded by a resection in 25 patients. The median total dose at re-irradiation was 54 Gy (range 8 - 60) as since 2009 a uniform protocol with 30x1.8Gy and concurrent temozolomide (TMZ) is used for non-stereotactic RT. 33.3% ($n = 22$) of patients received concurrent TMZ at re-irradiation. Response to treatment was assessed clinically and radiologically with MRI. Data were analyzed using the Kaplan-Meier method and Cox regression. RESULTS: At a median follow-up of 8.5 months, 67% of patients had died due to tumor progression. Median OS was 11.2 months with a median 6-month-OS of 71.5%. For primary GB median OS, 6-month OS and PFS, were 6.9 months, 55.8%, and 3.6 months and for secondary GB 14 months, 91.7% and 7.1 months, respectively. Clinical response (stable and/or improvement) to re-RT was 66.6%, compared to 91.8% after initial RT. Corticosteroids of 8.3% of patients could be tapered back to zero after re-RT. Acute toxicity within 3 months was mild to moderate (CTC 1 and 2). One patient developed a radiation necrosis which resolved later. Of 7 significant prognostic factors in univariate analysis only 2 factors remained significant in multivariate analysis: patients with an extended interval between initial RT and re-RT had a significantly longer OS and PFS ($p = 0.02$ and $p = 0.03$ respectively) and patients with corticosteroid dependency 3 months post-RT had a significantly worse OS and PFS ($p = 0.001$ and $p = 0.003$). For primary GBM alone an extended interval between initial RT and re-RT was a significant factor for both OS and PFS ($p = 0.005$) and clinical- and planning tumour volume were significant prognostic factors for PFS ($p = 0.01$). Preliminary results of a matched pair analysis between primary RT and Re-RT for patients with a primary GB (own institute, 1:2 match, gender and age) show a significant longer OS after Re-RT compared to palliative chemotherapy and best supportive care at a median follow-up of 7.3 months ($p = 0.003$). CONCLUSION: The interval between initial irradiation and re-irradiation is the main prognostic factor for survival after re-irradiation for patients with a glioma and more specifically a primary GB. Still, the prognosis of these patients remains sombre and quality-of-life after Re-RT should in addition prospectively be investigated.

P.105. SUNITINIB MALATE IN COMBINATION WITH LOMUSTINE FOR PATIENTS WITH TEMOZOLOMIDE REFRACTORY RECURRENT WHO-GRADE II/III GLIOMAS

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INTRODUCTION: Receptor tyrosine kinase signaling causes intense neoangiogenesis in high-grade gliomas (HGG). The VEGFR2, PDGFR-alpha

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and KIT genes are frequently amplified and expressed in HGG. Sunitinib is an oral small molecule tyrosine kinase inhibitor that inhibits multiple receptors (including VEGFR, PDGFR, and c-Kit). Sunitinib has no meaningful activity in mono-therapy for recurrent de novo glioblastoma. We investigated the combination of sunitinib and lomustine for the treatment of patients (pts) with temozolomide (TMZ) refractory recurrent WHO grade II and III glioma. PATIENTS AND METHODS: Pts with recurrent low grade and anaplastic glioma were recruited according to a 2-stage phase II design. A daily dose of 25 mg sunitinib for 28 consecutive days was administered, followed by a 14 days treatment interval. Lomustine (CCNU) was administred as a single dose (80 mg/m^2) on day 14 of a 6week cycle. T1 ± Gd and T2/FLAIR weighted MRI images were obtained every 6 weeks. 18FET-PET was performed at baseline and in patients showing response on MRI. **Thirteen** pts were enrolled (median age 40 (range 33-49); M/F 8/5; KPS 80-90: 8 pts, KPS 70-60: 5 pts). All patients had PD following at least surgery, RT and TMZ. In 7 patients, treatment was initiated at second recurrence, in 4 patients at third recurrence and in 2 patients at fourth recurrence. RESULTS: Most frequent AEs where fatigue (gr 2: n= 3; gr 3: n= 1), thrombopenia (gr 2: n= 1 gr 3: n= 3 gr4: n= 1)), neutropenia (gr 2: n= 2; gr3: n= 2; gr4: n= 2) and lymphopenia (gr 2: n = 1; gr 3: n = 2; gr 4: n = 1)). No serious skin toxicity or gastrointestinal symptoms was observed with the 25mg daily dosing regimen. In 5/13 patients, CCNU had to be discontinued because of adverse events. Treatment with sunitinib was continued in these cases without reoccurrence of adverse events. The best objective tumor response according to RANO criteria: 1 CR, 1 PR (not-confirmed) and 2 SD (disease control rate: 4/13= 30,8%). In the patient with CR, FET-PET also indicated metabolic response. Currently, 4 patients are alive (median follow-up of 6,7 months (range 2,1 -21 months). Median TTP is 1,8 months. One patient had a progression-free survival of 14,8 months, another patient had 20,5 months of PFS; one patients is still progression-free at the moment of writing (follow-up of 21 months). CONCLUSIONS: Sunitinib in combination with lomustine is associated with acceptable toxicity and has activity in patients with recurrent, temozolomide refractory, low-grade and anaplastic glioma. Long-term PFS is observed in a minority of patients. Predictive factors indentifying this sensitive population are needed for further clinical development of this investigational therapy.

P.106. UNUSUAL MASSIVE SPINAL METASTASES FROM A RECURRENT INTRACRANIAL GLIOBLASTOMA MULTIFORME

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Glioblastoma multiforme is a highly malignant primary brain tumor and is the most common primary malignancy of the central nervous system. Glioblastoma multiforme is a locally aggressive, invasive tumor that is resistant to therapy. Extracranial seeding of GBM is very rare. Spinal seeding of GBM metastasis is generally observed in autopsy series, but symptomatic spinal metastases from primary GBM are rarely reported. We present a case of glioblastoma multiforme with massive spinal spread that presented with paraplegia. CASE REPORT: A 23-year-old female patient was operated on for a cranial tumor 1.5 years ago, and the pathology result was reported to be GBM. Sudden-onset paraplegia developed during the follow-up period in this patient, who received radiotherapy and temozolomide therapy in the postoperative period without complaints. Sensory deficits below the level of T1 were detected during the neurological examination of the patient. Cranial and full spinal Magnetic Resonance Imaging examinations were performed on the patient. A left frontal relapse mass was detected during the cranial MRI (Figure 1). In cervical and thoracic spinal MRIs, multiple nodular mass lesions with intradural extramedullary localization were observed at the levels of C6-7 (24x10 mm), T4 (19x10 mm), T5-6 (36x12 mm), T7 (26x10 mm), and T10 (23x13 mm). The lesions were isointense in T1-weighted sequences, applying clear pressure to spinal cord, and were hyperintense in T2-weighted sequences. The thoracic spinal cord thickness increased, and pathological signal changes consistent with edema were detected. In addition, hyperintense seeding was observed inside of the cord on T2-weighted sequences at the level of T5-6 measuring 3x1 cm. Edema in the spinal cord between the levels of C3-4 and C6-7 levels and an extra-axial lesion of approximately 10 mm in diameter at the bulbous level were observed (Figures 2 and 3). The patient, who was planning to undergo whole spinal RT, was conscious and cooperative. The patient underwent medical treatment and RT and died within four months after the diagnosis. DISCUSSION: Metastases of the primary CNS tumors are rarely observed. GBM is the most common and most malignant primary brain tumor in adults. Spinal and extra-spinal metastases are rarely observed with this tumor that usually progresses with intracranial relapses. The observed frequency of GBM spinal metastases is different in clinical reports and in autopsy series. It has been reported that GBM can extraneurally metastasize to the lymph nodes, lungs, bones, liver, and other organs of the body. It is well known that tumors localized in the ventricles or very close to the cerebrospinal fluid, such as medulloblastoma, ependymoma, germinoma, and brainstem glioma, can spread via the CSF. Frequently, GBM recurs locally in the region it first appeared as a local invasion, but it rarely spreads via the CSF.

P.107. GLIOBLASTOMAS DO METASTASIZE

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BACKGROUND: Since the introduction of combined postoperative chemo-radiotherapy treatment, the median overall survival of patients with a glioblastoma has increased. With a greater overall survival, metastases are increasingly observed albeit still rare. Hereby we present three cases of metastasized glioblastomas. Clinical presentation: Case 1: A 48-year-old female with a primary intracranial temporally located glioblastoma (diagnosed 2008) presented 1 year after initial treatment with back pain and paraparesis. A MRI of the spinal cord showed extensive intramedullary mass lesions, reaching from C5-T2. Biopsy of the lesions confirmed a glioblastoma. Case 2: A 51-year-old male with a longstanding history (diagnosed 1995) of a frontally located low grade astrocytoma, which eventually transformed (in 2011) to a glioblastoma, presented with lymphadenopathy in the neck region. He did not have any clinical symptoms. Biopsy of the cervical lymph node confirmed metastasized glioblastoma. Further radiological whole body analysis by FDG-CT-PET additionally revealed osseous mass lesions in the pelvic region, suspect for metastatic lesions of the glioblastoma. Case 3: A 55-year-old female presented with sensory deficiency and ataxia. MRI of the spine confirmed a cervical located mass lesion reaching from C2-C6. No abnormalities were noted on a cerebral MRI. The cervical lesion was treated as a glioblastoma. Tumour progression was seen one year after treatment. Further radiological analyses were performed to rule out any spinal or cranial metastases. MRI of the cerebrum showed a frontal mass lesion, with aspects of a glioblastoma. CONCLUSIONS: Although metastases of glioblastomas are still rare, with increased median overall survival we should be alert when patients present with symptoms or signs as mentioned above.

P.108. MOLECULAR MECHANISMS OF ACQUIRED RESISTANCE TO TEMOZOLOMIDE IN GLIOBLASTOMA

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Temozolomide is the first chemotherapeutic agent that has shown to prolong the survival of patients with glioblastoma, damaging the tumor DNA by alkylation/methylation of guanine residues. This effect is counteracted by the expression of the DNA repair protein O6-methylguanine-DNA methyltransferase (MGMT) in tumor cells. MGMT is epigenetically silenced in about 40% of all glioblastomas, correlating with a better benefit from alkylating chemotherapy. However, even patients with MGMT promoter methylation suffer from tumor progression eventually. Here, we generated glioma cells with acquired resistance to temozolomide, aiming at identifying the underlying mechanisms leading to secondary therapy failure. A stable phenotype of resistant sub-cell-lines was generated by repetitive exposure of different glioma cells to increasing concentrations of temozolomide. In LN-18 cells which constitutively express MGMT, we observed a strong up-regulation of MGMT levels in the resistant cells, while no de novo expression of MGMT was detected in the MGMT-negative cell lines LNT-229_R or LN-308_R. In contrast, resistant LNT-229 cells display a strong down-regulation of several mismatch-repair (MMR) genes. Using RNA interference, we silenced the expression of single MMR genes in parental LNT-229, which confirmed the role of MMR proteins for acquired TMZ resistance. No obvious mechanism of resistance was identified in the third cell line, LN-308, except for reduced methylation of LINE-1 repetitive elements. In summary, we demonstrate the contribution of different molecular mechanisms to the development of acquired TMZ resistance in glioma cells. Therefore, distinct strategies to overcome temozolomide resistance need to be developed.

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P.109. INCIDENCE AND OUTCOME OF SYMPTOMATIC VENOUS THROMBOEMBOLISM IN PATIENTS WITH GLIOBLASTOMA MULTIFORME IN SOUTHERN ALBERTA

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PURPOSE/OBJECTIVE: Patients with malignancy, and especially those with Glioblastoma Multiforme (WHO grade IV), have an increased risk of venous thromboembolism (VTE). The incidence of VTE reported in the literature has been highly variable and few studies have carefully investigated the factors related to the development of VTE and its impact on patient outcome in this population. The objective of this study was to determine the incidence of symptomatic VTE, to identify clinical and molecular factors related to VTE formation, and to determine outcome in this patient population. MATERIALS/METHODS: We conducted a 5-year retrospective analysis of data obtained in all cases of Glioblastoma Multiforme diagnosed in Southern Alberta between 2005 and 2009, and patients who were treated with radical radiotherapy and chemotherapy concurrently. The occurrence of a VTE was identified using linked hospital discharge data and a province-wide pharmacy network record. RESULTS: Among 116 cases, the incidence of symptomatic VTE was 18.1% (21 cases). All patients were treated with either low molecular weight heparin ($n = 15$) or warfarin ($n = 6$). O6-methyl guanine methyl transferase (MGMT) methylation status was not associated with the development of symptomatic VTE. However, the methylated patients continued to have better overall survival (15.7 months vs 12.4 months, $p = 0.047$). In patients who developed a symptomatic VTE, there was no statistical change in survival ($p = 0.88$) or local control ($p = 0.60$). CONCLUSIONS: Symptomatic venous thromboembolism is common in patients with glioblastoma multiforme but does not affect local control or overall survival in GBM patients. Warfarin instead of LMWH was still used in a significant number of patients for anticoagulation. MGMT methylation status continues to predict longer overall survival in patients who develop symptomatic VTEs.

P.110. ACUTE HYPOXIA INDUCES SPECIFIC CHANGES IN MIRNA EXPRESSION OF STEM-LIKE GLIOMA CELLS

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Tumour hypoxia and presence of tumour stem cells are related to therapeutic resistance and tumorigenicity in glioblastomas. Research findings within the new field of microRNA (miRNA) and cancer suggest that miRNAs represent a new generation of therapeutic targets, but knowledge of the interplay between miRNAs and tumour stem cell biology under hypoxia is limited. The aim of the present study was therefore to identify deregulated miRNAs in acute hypoxia and to identify possible associated early changes in the expression of stem cell markers. Glioma stem cell-containing spheroid (GSS) cultures as well as spheroids obtained from commercial cell lines (CCL) were cultured in stem cell medium at either 2 % or 21 % oxygen for 24 hours. MiRNA profiling, recognizing 1294 human miRNAs, revealed different profiles for the individual cell lines by hierarchical cluster analysis, and differences were especially evident between GSS and CCL spheroids. Among 10 significantly deregulated miRNAs, miR-210, miR-1908, and miR-4327 were up-regulated in hypoxic GSS cultures. Using an immunohistochemical panel of 10 stem cell markers (CD133, CD15, Nestin, Musashi, Bmi-1, Oct-4, SOX2, ID1, ALDH1, and Podoplanin), we found no systematic up-regulation as earlier found in long-term hypoxia. This suggests that the change into a more stem cell-like phenotype is obtained by hypoxia-induced dedifferentiation of proliferating cells more than by an immediate change of already existing cells. In conclusion, this study shows that acute hypoxia induces specific changes in the miRNA expression of stem-like glioma cells. We found no acute hypoxia-induced systematic up-regulation of stem cell markers as earlier found in long-term hypoxia.

P.111. RELEVANCE OF AGE AND MGMT STATUS FOR OUTCOME IN ELDERLY GLIOBLASTOMA PATIENTS TREATED IN A NEUROONCOLOGICAL CENTER: DIFFERENT RESULTS IN COMPARISON TO CLASSICAL PROGNOSTIC FACTORS

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OBJECTIVE: To investigate independent prognostic factors for outcome in elderly patients with glioblastoma in correlation with therapeutic strategies. METHODS: We retrospectively reviewed 117 patients with newly diagnosed glioblastoma from our database between 1997 and 2010. Patients were divided into two cohorts: ages 60-69 and ≥ 70. The association to patient survival was estimated using log-rank test for univariate analysis and cox regression method for multivariate analysis. RESULTS: Median patient age was 69 years (range: 60-85 years). The median postoperative Karnofsky Performance Score (KPS) was 80. Total tumor resection was performed in 47 cases (40%), subtotal removal in 58 cases (49%) and biopsy in 12 patients (10%). Treatment after surgery contains radiation therapy (80%), concomitant Temozolomide (65%) and adjuvant chemotherapy (43%). Median Overall survival in cohort 60-69 years was 16.4 months and 10.0 months in patients ≥ 70. The following parameters were significantly associated with survival in univariate analysis: age with significant difference between the two cohorts, total resection, KPS and kind of treatment (more than surgery alone). MGMT status was not significant for survival. The following parameters were significantly associated with survival in multivariate analysis: Only KPS and treatment were significant independent prognostic factors for survival. CONCLUSION: In contrast to younger patients, age and MGMT status are not prognostic relevant for survival outcome in a solely old patient population. Treatment which includes more than surgery alone independent of the kind of therapy (radiotherapy or combined radio-chemotherapy) and functional age (KPS) is crucial in elderly glioblastoma patients.

P.112. ANGIOTENSIN-II INHIBITORS HAVE A STEROID-SPARING EFFECTS IN GLIOBLASTOMA PATIENTS

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BACKGROUND: The standard of care in glioblastoma (GBM) patients relies on surgical resection, radiation therapy (RT) and temozolomide. Steroids are required in almost all patients to reduce peritumoral edema, but are associated with numerous side effects. Vascular Endothelial Growth Factor (VEGF) is a key driver of peritumoral edema and angiogenesis in human GBM. Recently, Angiotensin-II inhibitors were reported to reduce VEGF secretion and tumor growth in some animal models. METHODS: In order to investigate whether Angiotensin-II inhibitors might have a similar effect in humans, we retrospectively investigated a series of 87 consecutive, newly diagnosed GBM patients, treated in a single center. Among these patients, 29 (33%) were already treated before RT for high blood pressure, 18 of them (21%) with an Angiotensin-II inhibitor. In all patients, performance status, surgical procedures, and steroid dosages were documented. RESULTS: Patients treated with Angiotensin-II inhibitors, but not other anti-hypertensive drugs, required half of the steroids of the other patients during radiotherapy ($p = 0.005$ in multivariate analysis, considering other antihypertensive treatments, surgical resection and performance status). This effect of Angiotensin-II inhibitors was also significant at the beginning of radiotherapy ($p = 0.03$ in multivariate analysis). Treatment with Angiotensin-II inhibitors had no effect on survival (16.2 vs. 17.9 months for the treated and the non-treated group, respectively, $p = 0.77$). CONCLUSION: Angiotensin-II inhibitors might display significant steroid-sparing effects in brain tumor patients. Given the morbidity associated with steroids, this finding might have important practical consequences in these patients and warrants a randomized study.

P.113. MOLECULAR AND CELLULAR EVENTS INVOLVED IN THE ACTION OF TEMOZOLOMIDE IN TUMORAL GLIAL AND VASCULAR CELLS ISSUED FROM GLIOBLASTOMAS

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Glioblastoma (GBM) is the most agressive brain tumor. Despite surgery, radiotherapy, and temozolomide (TMZ)-based chemotherapy, the prognosis of patients remains poor and the resistance to TMZ is a barrier to effective

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therapy. Although the presence of MGMT is known to alter TMZ efficacy, MGMT-independent mechanisms are also involved in chemoresistance. Our aim is to analyse the molecular mechanisms involved in TMZ-resistance in GBM. Our data indicate that TMZ decreases the proliferation of a number of tumoral glial cell lines (U87, U373, T98G). Conversely, the proliferation of U138 and LN18 cell lines is not affected by TMZ. Variable growth responses are also observed in primary culture of glial cells issued of GBM. Whereas TMZ is uneffective on most of the cultures, a moderate inhibition associated with an accumulation in G2/M cell cycle phases is observed in a number of cases. The effect of TMZ has also been examined on normal endothelial cells as well as on vascular cells issued from GBM. TMZ inhibits normal endothelial cell growth but fails to decrease the proliferation of GBM vascular cells, indicating fondamental differences in normal vs tumoral vascular cells. Activation of signaling pathways is an alternative mechanism for TMZ resistance. An activation of ERK1/2 by TMZ is observed in GBM primary cultures that display growth-resistance to TMZ. Moreover, the inhibition of ERK1/2 make a number of primary cultures responsives to TMZ, suggesting that ERK signaling might be involved in TMZ resistance. MicroRNAs (miRNAs) play a role in radio/chemotherapy responsiveness. Among them, miR21 is described as pro-tumoral, whereas miR200a is a growth-regulatory factor. We show that Mir21 is overexpressed in tumoral cell lines and GBMs as compared to low grade tumors. Conversely, miR200a is overexpressed in low grade tumors vs tumoral cell lines and GBMs. Inhibition of miR21 or overexpression of miR200a by oligonucleotide transfection in U87 cell line does not modify basal cell proliferation. However, TMZ is more effective on cell proliferation when U87 cells are transfected with miR21 antisens or miR200a mimic, indicating that miR21 and miR200a are both involved in GBM progression and in TMZ responsiveness. Studies are in progress to compare miRNA expression in low vs high grade brain tumor, in order to identify miRNA involved in GBM progression. Potential miRNA targets will be examined to characterise genes and signaling pathways responsible for chemoresistance.

P.114. GENETIC ALTERATIONS IN GLIOMA BY USING SNIP-MICROARRAY

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PURPOSE: Glioma is a CNS tumor resulting from accumulation of genetic. alterations. Whole genome analysis clarifying the correlations between genetic abnormalities and clinical features in gliomas may provide a new strategy for determining prognosis and treatment of glioma patients. PATIENTS AND METHODS: A robust technology, single nucleotide microarray(SNP-chip) was used for the whole genome analysis in all grade gliomas. We examined 128 samples with GBM, 93 with grade III glioma, 31 with low grade glioma andtheir matched blood samples at 50000/250000 SNP sites using an SNP-chip platform. Correlations between genetic alterations and prognosis in malignant gliomas were also analyzed. In this analysis we focused on several genetic alterations such as loss of heterozygosity (LOH) of chromosome 10, 1p, 19q, amplifications sites of PI3KC2B, PDGFRA, EGFR and LOH of CDKN2B locus on chromosome 9p21, p53 locus on 17p13, RB locus on 13q14. RESULTS: Genetic alterations in the genes on the signal of growth factor. receptors /RAS/PI(3)kinase/PTEN, on the signal of G1 check point and on the signal of p53 were detected in 89%, 89% and 75% of GBM, in 35%, 36%,42% of grade III glioma, respectively. Genetic alterations were detected approximately 10 ~ 20% of low grade gliomas, however, no genetic alteration was found in pilocytic astrocytoma. EGFR amplification and whole LOH of chromosome 10 were dismal prognosis factor in GBM and grade III gliomas. In glioblastoma with oligodendroglial components (GBMO) the similar genetic alterations with GBM were observed. CONCLUSION: Although there are various genetic alterations, common genetic alterations were observed in all grades of gliomas. Whole genome analysis was very useful for the prognostic information in the patients with all grades of gliomas.

P.115. PROGNOSTIC FACTORS FOR WHO GRADE III GLIOMAS: A SINGLE INSTITUTION ANALYSIS

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BACKGROUND: Anaplastic astrocytoma (AA), anaplastic oligodendroglioma (AO), and anaplastic oligoastrocytoma (AOA) are the major histological categories of WHO grade 3 gliomas. Most randomized trials pool both grades III or IV gliomas in their analysis. Consequently, there is limited data on specific prognostic factors for patients with grade III gliomas outside of 1p19q co-deletions. METHODS: After obtaining IRB approval, the Cleveland Clinic Brain Tumor and Neuro-Oncology Centers database was used to identify patients with histologically confirmed grade III glioma at the time of diagnosis. Multivariable analysis was conducted to identify independent predictors of survival independent of 1p19q status using a Cox proportional hazards model and a stepwise selection algorithm that used $p < .10$ as the criteria for entry and $p < 0.05$ for retention. RESULTS: Chart records of 336 pts (52% of whom were men) diagnosed between 1994 and 2009 were included for analysis. The median age at presentation was 50 years (range, 1-88 years). 49% of pts had biopsy only, 21% had gross total resection (GTR), 5% had near total resection (NTR), and 25% had subtotal resection (STR). Following surgery, 92% of pts underwent radiation and 62% underwent concurrent chemotherapy. Median overall survival (OS) of AA, AOA, AO was 17.0 months, 58.7 months and 74.2 months respectively. Median OS for all pts was 25.9 months. Five factors were identified as predictors of overall survival independent of 1p19q status; age at diagnosis ($p < 0.001$), Karnofsky Performance Status ($p < 0.001$), histology (AA vs. AO, $p < 0.001$), multifocal disease ($p = 0.012$) and type of surgery (GTR vs. biopsy, $p < 0.001$). CONCLUSIONS: Independent of 1p19q status, older age, poor performance status, AA or AOA histology, and multifocal disease were associated with higher mortality. GTR or STR, relative to biopsy, was associated with lower mortality.

P.116. EGFR GENE VARIANTS ARE ASSOCIATED WITH SPECIFIC SOMATIC ABERRATIONS IN GLIOMA

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There are a number of gene variants that have been associated with an increased risk of developing glioma. We hypothesized that the reported risk variants may be associated with tumor genomic instability. To explore potential correlations between germline risk variants and somatic genetic events, we analyzed matched tumor and blood samples from 95 glioma patients by means of SNP genotyping. The generated genotype data was used to calculate genome wide, allele specific, copy number profiles of the tumor samples. We compared the copy number profiles across samples and found two EGFR gene variants (rs17172430 and rs11979158) that were associated with homozygous deletion at the CDKN2A/B locus. One of the EGFR variants (rs17172430) was also associated with loss of heterozygosity at the EGFR locus. Our findings were confirmed in a separate dataset consisting of matched blood and tumor samples from 300 glioblastoma patients, compiled from publically available TCGA data. These results imply there is a functional effect of germline EGFR variants on tumor progression.

P.117. OUTCOME EVALUATION IN GLIOBLASTOMA PATIENTS OLDER THAN 65 YEARS: A RETROSPECTIVE SINGLE CENTER STUDY

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BACKGROUND: The NCT00820963 trial, the Nordic Glioma Study (NGS) started in 2003 to investigate an experimental radiotherapy scheme with 10x 3.4 Gy vs. chemotherapy with Temozolomide (TMZ) 200 mg/m^2, days 1-5 for 6 cycles vs. radiotherapy with 60 Gy in 30 fractions for elderly patients with newly diagnosed glioblastoma. In this retrospective study, we evaluated the outcome of patients with primary GBM, aged $\geq$65 years, treated in our institution during the period of recruitment for the NGS study (2003-2009), to which our site contributed 35 patients. PATIENTS: The study population of 70 patients, 32 women and 38 men, aged 65 to 83 years, median 71 years, was divided into three groups: the NGS group consisted of 35 patients with13 patients in the standard radiation therapy arm with 60 Gy, 12 patients in the hypofractioned radiation therapy arm with 34 Gy and 10 patients in the TMZ arm. The other group of 35

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patients consisted in 23 fit elderly patients in the RCT arm who were treated with standard radiochemotherapy (RCT) like younger GBM patients and 12 frail patients who mostly started radiotherapy with 60 Gy but did not receive chemotherapy (nonRCT arm). RESULTS: 31 of the 70 patients underwent gross total resection (44%), 21 patients had subtotal resection (30%) whereas 18 patients underwent biopsy (26%). The median overall survival in the three study arms of the NGS group in particular was 6.0 months in the 60 Gy arm, 7.0 month in the hypofractioned 34 Gy arm and 10.0 months in the TMZ arm ($p = 0.012$). The median overall survival in the RCT group was 21.0 months vs. 3.0 months in the nonRCT arm. Functional independence. Karnofsky scores were evaluated in three months interval. The median time to the loss of functional independence (KI 60%) was > 6 months in RCT patients, 6 months in the NGS group and less than three months in nonRCT arm. No grade 3 or 4 toxicities were documented in the 60 Gy and 34 Gy arm of the NGS group. In the TMZ arm 2 of 10 patients (20%) suffered from grade 3 or 4 thrombocytopenia. In the RCT group grade 3 haematologic toxicity (thrombocytopenia and leucopenia) occurred in 2 of 23 patients (8.7%) and in one patient of the nonRCT arm (8.3%), probably due to dexamethasone. CONCLUSION: This retrospective single center experience shows the wide variety of outcomes in elderly patients with GBM and underlines the need for individualized, geriatric assessment based therapy planning, performance and follow up.

P.118. THROMBOSPONDIN-1 (THBS-1) AS A MAJOR LINK BETWEEN METABOLISM AND MIGRATION IN HIGH-GRADE GLIOMAS

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INTRODUCTION: Glioblastomas (GBM) are associated with poor prognosis due to their highly invasive phenotype, their severe local immunosuppression and their characteristical changes in tumor metabolism. One key metabolic enzyme of aerobic glycolysis, namely the Warburg effect, is lactate dehydrogenase A (LDH-A), catalysing the reaction of pyruvate into lactate. Higher levels of lactate lead to acidification of the tumor environment and promote tumor cell migration. Thrombospondin-1 (THBS-1) is a matricellular molecule playing a major role in the activation of Transforming growth factor beta 2 (TGF-beta2). TGF-beta2 is a key regulator of glioblastoma cell invasion, angiogenesis and local immunosuppression. METHODS: LDH-A and THBS-1 knock-down was performed using transient transfection of glioma cells and brain tumor initiating cells with small interfering RNA directed against LDH-A (siLDH-A) and THBS-1 (siTHBS-1). Western Blot, qRT-PCR, and ELISA were used to investigate expression levels of TGF-beta2 and THBS-1 in siLDH-A transfected cells. Migration of transfected cells was investigated by scratch and Boyden Chamber assays. Synthetic THBS-1 polypeptide was used to examine the role of THBS-1 addition to siLDH-A transfected cells. Lactate, lactic acid and hydrochloric acid were added to GBM cells to investigate lactate regulatory effects in contrast to LDH-A effects. RESULTS: siLDH-A leads to decreased expression of THBS-1 and TGF-beta2 on the mRNA and protein level. Migration of tumor cells is impaired by siLDH-A and siTHBS-1. Addition of synthetic THBS-1 polypeptide to siLDH-A transfected cells can rescue TGF-beta2 protein expression and tumor cell migration. Addition of lactate and lactic acid, but not hydrochloric acid to GBM cells increases significantly THBS-1 expression on the mRNA and protein level. TGF-beta 2 expression is enhanced by lactate on the protein level and on the mRNA level in long-term assays, resulting in increased migration of tumor cells. DISCUSSION: Our data indicate that increased or decreased levels of lactate correlate with THBS-1 and TGF-beta2 expression, showing a link between aberrant glioma metabolism and migration. We hypothesize that this interaction is mediated by lactate-responsive-elements, namely the transcription factors ets-1 and AP-1, that bind to the promoter of THBS-1, which in turn activates proinvasive TGF-beta2. Independently, THBS-1 may also activate glioma migration through the upregulation of u-PA and u-PAR in a TGF-beta2 independent way.

P.119. PENAO: A POTENT ARSENICAL-BASED INHIBITOR FOR GLIOBLASTOMA

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PENAO, (4-(N-(S-penicillaminylacetyl)amino) phenylarsonous acid) is a mitochondrial agent that inactivates inner-membrane adenine nucleotide translocase (ANT). PENAO blocks ANT delivery of ATP to mitochondrial-bound hexokinase II, thus inhibiting glucose metabolism and triggering the mitochondrial permeability transition pore which results in proliferation arrest and apoptotic cell death. We tested the efficacy of PENAO on a panel of 13 glioblastoma cell lines (including commercial and treated and untreated primary lines) which differed in tumorigenicity, drug resistance, invasion and DNA repair. PENAO demonstrated impressive anti-proliferative activity. The half-maximal inhibitory concentration (IC_{50}) values for PENAO were in the range of 0.3-4.5 μM for glioma cells. Up to 440-fold higher anti-proliferative activity was observed for PENAO when compared to temozolomide. PENAO concentrations of 0.3-5 μM induced the intrinsic apoptosis pathway, which was evident under both normoxic and hypoxic (1%) conditions. PENAO was also able to inhibit glioblastoma cellular migration and invasion at concentrations of 1.4 μM, independent of cellular proliferation or viability. When anti-proliferative activities of PENAO were compared with its effects on normal human foetal lung fibroblast (MRC5), PENAO showed selectivity for glioblastoma cell lines ranging from 4 to 49. PENAO is a substrate of the multidrug resistant associated proteins ABCC1 and ABCC2. PENAO anti-proliferative activity was enhanced by 2 to 8-fold with the inhibition of these transporters. Concomitant inhibitions of the transporters and cellular glutathione synthesis, increased PENAO efficacy by up to 100-fold in established cell lines and by up to 20-fold in primary glioma cells. PENAO exerts its effect on the glycolytic pathway as evidenced by the ability of PENAO to inhibit cellular acidic levels (lactate production) in tumour cells, at an IC_{50} of 1.5 μM. Concurrently, oxygen utilisation was also inhibited as well as an increase in the cytosolic levels of super oxide and the disruption of the mitochondrial transmembrane potential resulting in the induction of the intrinsic apoptosis pathway. In vivo administration of 1mg/kg/day PENAO to 10 mice bearing subcutaneous glioblastoma resulted in 8 partial and 2 complete responses. There were no signs or symptoms of treatment toxicity. Orthotopic xenotransplanted mouse model demonstrated that PENAO can readily cross the intact blood-brain- barrier and can accumulate to a higher extent in brain tumor tissue. Efficacy studies are currently underway. The efficacy of PENAO in *in vitro* and *in vivo* models of glioblastoma has been highly promising and human clinical trials has been initiated this year for the determination of safety and blood-brain barrier permeability within glioblastoma patients.

P.120. TREATMENT OF HIGH GRADE GLIOMAS IN ELDERLY PATIENTS

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BACKGOUND: treatment of high grade gliomas in elderly patients is not well established. Elderly patients are frequently excluded from aggressive multimodal treatment for concerns of increased morbidity. We present our results in treatment of patients over 65 years with different type of high grade gliomas. PATIENTS AND METHODS: there have been 65 patients with median age 69 years (range 65-81) treated between 2005 and 2010; female/male ratio: 37/28. Type of tumor was glioblastoma multiform 66.6 %, anaplastic astrocitoma 10.61 %, oligoastrocitoma and oligodendroglioma grade 3. Surgery was performed in all patients: complete resection in 50 (76.9%) patients, subtotal resection in 13 (20%) patients and 2 biopsies (3.1%). Postoperative 3D conformal radiotherapy was performed with two different type of fractionation: standard fractionation in 22 patients with TD= 40-60 Gy, mean dose 56 Gy and hypofractionation with TD= 3-45 Gy, mean dose 32 GY. Concomitant and adjuvant chemotherapy with Temozolomide was done in 33.33% of patients, concomitant chemotherapy with radiotherapy in 22.75 % of patients and without chemotherapy were 37.88% of patients. At the beginning of radiotherapy neurological index was 0-1 for 28 (43.1%) patients and 2-3 for 37 (56.9%) patients. RESULTS: at study evaluation there were 55 deaths and 10 patients alive (median follow-up 32.6 months). Median overall survival at 36 months for the entire cohort was 13% (CI: 7%-25%). For patients with glioblastoma and anaplastic astrocitoma was 8% and 43% for patients with other histological type. Survival rates at 24 moths was 45% for patients with concomitant and adjuvant chemotherapy and 21% for patients who performed concomitant or adjuvant chemotherapy alone. Although at 36 moths the difference are no significant. After concomitant radiochemotherapy acute toxicity haematologic and digestive was grade 1 in 4.6% and 13.6%; grade 2: 4.6%; 4.6% and grade 3.6%. Majority of patients have no toxicity (86.4% and 81.8%). Survival at 36 months for patients with standard radiotherapy was 20% versus 9% for patients treated with hypofractionation ($p = 0.02$). CONCLUSION: radio-chemotherapy is possible in elderly patients with mild toxicity and good results. Patients who can perform radio-

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chemotherapy concomitant and adjuvant live longer. Combined treatment was well tolerated, despite the type of radiotherapy and is a good option for elderly patients.

P.121. OUTCOME OF GBM PATIENTS DIAGNOSED BEFORE THE AGE OF 40 YEARS: A SINGLE INSTITUTION RETROSPECTIVE STUDY

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BACKGROUND: Young age is well-known as favorable prognostic factor for patients with glioblastoma multiforme (GBM). In this retrospective study we reviewed the outcome of "young" patients with newly diagnosed GBM, defined arbitrarily as GBM diagnosed before the age of 40 years. Patients and Methods. Data of 47 histologically proven newly diagnosed primary GBM patients were retrospectively analysed. The 28 men and 19 women were aged between 18 and 39 years, in median 32 years. All were treated at the Medical University of Vienna between January 2003 and December 2010 with focal radiation up to 60 Gy, concomitant and adjuvant chemotherapy. IDH 1 mutation status was retrospectively analyzed in 37/47 samples by immunohistochemistry. Moreover, tumour samples were tested for MGMT promoter methylation. The primary endpoint was the survival analysis including overall survival (OS) and time to tumour progression (TTP) in accordance to already established prognostic factors. RESULTS: Median OS and TTP were 27.9 months (8- 100+ months) and 16.6 months (4-53+ months) respectively. The most striking finding was the unexpected high prevalence of IDH1 mutation among young patients with primary GBM (17 of 33 tested patients) and its strong impact on OS with 36.2 months versus 20.6 months (Hazard Ratio 0.262). Patients with methylated MGMT promoter also showed a favourable survival duration with 32 months versus 22 months for patients with unmethylated MGMT promoter. Of note, the social and economical situation of the young GBM patients was alarming, as only a minority of patients (17%) succeeded to stay employed after receiving the diagnosis. CONCLUSIONS: The growing importance of molecular-genetic markers was shown by means of the IDH1 mutation and the MGMT methylation status. There is a chance of achieving improvement in the overall survival of patients with GBM by focusing the prospective investigations on an increased adaption of therapy to molecular genetic changes. The social and economical coverage of glioma patients remains an unsolved societal problem.

P.122. TNF-PATHWAY UPREGULATION IN GLIOBLASTOMA MULTIFORME

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Glioblastoma Multiforme is a malignant and invasive tumor that arises from glial cells in the central nervous system. Ligands and receptors of the tumor necrosis factor (TNF) super-family, regulate several cellular responses including proliferation, differentiation, migration, and induction of apoptosis. Various studies have been carried out in recent years to explore the roles of TNF members in glioblastoma -mostly related to invasion of adjacent healthy tissues-, so our aim is to determine the expression pattern of 40 TNF members by microarrays and validate the findings by RT-qPCR. Total RNA from 15 frozen glioblastomas was extracted with QIAGEN RNeasy Mini Kit (Valencia, CA, USA). Four controls were used. GeneChip® Human Gene 1.0 ST Array from Affymetrix (CA, USA) with 28,132 gene-level probe sets with Ensembl support was selected to perform this study. Forty genes of the array related to TNF pathway were selected for the analysis. Quantitative assay was performed using ABI PRISM 7900HT Sequence Detection System (Applied Biosystems, Foster City, CA). Values were calibrated according to the ΔΔCT method, and relative quantity (RQ) values were calculated. GAPDH was used as endogenous control to normalize. TaqMan® expression assays of the following genes were used: GAPDH, BIRC5 (for positive control) TNF, TNFRSF10B and TNFRSF1A. Eighteen genes of the TNF superfamily were deregulated by the arrays in glioblastomas. Of these, 17 were upregulated at $p > 0.05$ (TNFAIP6, TNFAIP3, TNFRSF10C, TNF, TNFRSF14, TNFSF15, TNFRSF11B, TNFSF8, TNFRSF10B, TNFRSF10D, TNFAIP2, TNFRSF12A, TNFRSF19, TNFSF13B, TNFRSF1A, TNFRSF1B, TNFAIP8L2), and one of them (TNFAIP8L1) was downregulated. TNF, TNFRSF10B and TNFRSF1A were validated as upregulated by RT-qPCR. BIRC5 was upregulated in all tumors. Control samples and tumors showed differences in grouping by PCA and hierarchical clustering. These results agree with previous studies on several of the TNF members (i.e. TNFRSF10B, TNFRSF19 or TNFRSF12A). According to our data, some members of the super-family TNF show upregulation, so treatment based on specific upregulated TNF genes could be an alternative approach for the treatment.

P.123. COMBINATION OF PERITUMORAL ADMINISTRATION OF CPG-ODN WITH IMMUNIZATION AGAINST VEGF FOR THE TREATMENT OF MALIGNANT GLIOMA

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INTRODUCTION: VEGF plays a key role in tumor angiogenesis. Bevacizumab, a monoclonal antibody against VEGF, has demonstrated its efficacy and has reached approval in several cancers as an anti-angiogenic agent. Interestingly, VEGF might also play a role in the recruitment of Myeloid Suppressing Cells that infiltrate the tumors and induce immune tolerance. CpG-ODN are well-known immunostimulatory oligonucleotides, that activate antigen-presenting cells and B-cells. When injected locally, they induce immune rejection of established tumors in various syngenic animal models. Clinical trials are on-going. This study assessed the efficacy of a regimen combining CpG-ODN and immunization against VEGF in a curative murine model of glioblastoma. METHODS: Fisher rats ($n = 12$/groups) bearing subcutaneous syngenic RG2 gliomas received two peritumoral injections of 100 μg CpG-ODN (at two-week interval) combined (or not) with distant subcutaneous immunizations against VEGF. Serum anti-VEGF antibodies were assessed by Western-Blot, 3 weeks after immunization. Tumor growth and survival were monitored. RESULTS: **1/ VEGF immunization induced circulating anti-VEGF antibodies**. After 2 immunizations with human VEGF, 67 % of the rats developed significant anti-human VEGF antibody titres. Interestingly, 50 % of the rats also developed anti-rat VEGF antibodies, showing that our vaccination protocol was able to break tolerance. 2/ VEGF immunization slightly reduced tumor growth: A moderate, but significant, tumor growth inhibition was observed when rats were immunized against VEGF 5 days, but not 7 days, after tumor graft ($p = 0.013$, $n = 12$ rats per group). Therefore, anti-VEGF immunization can slow tumor growth, provided this immunization starts when the tumor size is still limited. 3/ VEGF immunization is synergistic with local CpG-ODN immunotherapy: When rats were treated by two peritumoral injections of CpG-ODN at two-week interval, starting 7 days after tumor challenge, a tumor growth inhibition was observed ($p < 0.01$ for untreated vs CpG-ODN-treated rats). This antitumor effect was further enhanced when the CpG-ODN treatment was combined with an anti-VEGF immunization ($p < 0.01$ for CpG-ODN-treated vs CpG-ODN + anti-VEGF-treated rats, $n = 12$ rats per group). CONCLUSION: As already known, local treatment with CpG-ODN is efficient in the RG2 glioma model. Interestingly, immunization against VEGF can both induce anti-VEGF antibodies and tumor growth inhibition when the tumor size is limited. This immunization against VEGF acts synergistically with local CpG-ODN for the treatment of established tumors. Optimisation of the protocol, efficacy on other tumor types, and identification of the mechanisms underlying this synergy are on-going.

P.124. MOLECULAR BIOMARKERS WITH PREDICTIVE VALUE IN GLIOMA PATIENTS

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Brain tumours, especially glioblastomas, are one of the most aggressive tumours which are characterized by high mortality rate. Several predictive molecular markers have been associated with this type of cancer.

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Isocytrate dehydrogenases (IDHs) are a family of enzymes which catalyze oxidative decarboxylation of isocytrate into α-ketoglutarate. Somatic mutations in IDH1 or IDH2 genes (encoding cytosolic and mitochondrial NADP-dependent IDHs, respectively) have been described in glial tumours of younger patients. They are commonly found together with chromosomal deletion of the short arm of chromosome 1 (1p) and the long arm of chromosome 19 (19q) and are associated with good prognosis for the patients. Another gene with favourable prognostic/ predictive value is O6-methylguanine-DNA methyltransferase (MGMT). It encodes a protein that repairs the cytotoxic and mutagenic O6-alkylguanine produced by alkylating agents such as chemotherapeutic agents and mutagens. To determine the prevalence of aberrations and their prognostic value 100 glial tumours, including astrocytomas and oligodendrogliomas of various grades, were analyzed. IDH1 and IDH2 mutations were examined by direct sequencing of exon 4 of both genes. Also, genomic DNA was bisulfite converted and the samples were analyzed for promoter hypermethylation of MGMT gene using Methylation-Sensitive High Resolution Melting (MS-HRM). Samples with aberrations in IDH1 or IDH2 were also screened for 1p/19q loss by MLPA technique. IDH1 genetic alterations were found in 21 (21%) glial tumours of WHO grade II, III and IV. In 20 patients mutations were G-to-A changes at position 395 (amino acid substitution R132H) and in one patient G-to-T change at position 395 (amino acid substitution R132L) was observed. A mutation in IDH2 was detected in only 1 tumour. Genetic alterations in IDH1 and IDH2 were associated with increased overall survival (median survival 101.1 months vs. 17.9 in non-mutated cases; $p < 0.0001$). In the group of patients with IDH1 and IDH2 mutations, MLPA analysis showed loss of 1p and/or 19q in 62 % of cases and MS-HRM analysis demonstrated hypermethylation of MGMT gene in 7 patients (68 %). However, no statistical significance was reached for the association of 1p19q co-deletion or MGMT methylation with the overall survival of patients with gliomas. Our results indicate that IDH1 and IDH2 genetic alterations are common in glial tumours with prolonged survival and may be used as specific prognostic biomarkers in patients with gliomas.

P.125. TUMOUR-INITIATING CELLS IN HUMAN GLIOBLASTOMA ARE HETEROGENEOUS POPULATIONS WHICH RESIDE IN DISTINCT ENVIRONMENTAL NICHES

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We previously demonstrated that it is possible to objectively interrogate human glioblastoma (GBM) by using 5-aminolevulinic acid (5-ALA), an endogenous intermediate of the porphyrin biosynthesis pathway. It acts as a prodrug that is metabolised intracellularly leading to the selective accumulation of the fluorescent molecule protoporphyrin IX (PpIX) in tumour cells. Tumour tissue resection is then performed on a fluorescence-guided basis allowing direct visualization of tumour tissue and diffusely infiltrative disease. This approach gave us the possibility to identify and characterize tumour compartments in GBM. We have now interrogated tumour compartments based on PpIX fluorescence. Our results demonstrate that: 1) cells residing in the tumour margin do not resemble the "cancer stem cell" phenotype but are tumorigenic to some extent, 2) fluorescent material is present in the SVZ of 65% of our GBM ($n = 65$ patients), 3) it is possible to isolate tumour-initiating cells (TICs) from these SVZs. These cells are phenotypically similar to those isolated from the tumour mass and possess all the "cancer stem cell" cardinal features, 4) SNP analysis of SVZ tissue samples reveals distinct genetic aberrations, 5) TICs in the SVZ reside in a pro-angiogenic environment. Further characterization of niches in tumour edges and SVZ as well as response to chemotherapeutic agents is in progress to highlight intratumour heterogeneity of TICs.

P.126. MK-2206 ON GLIOMAS - INTERACTION WITH RADIATION AND TEMOZOLOMIDE

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Seven malignant glioma cell lines were cultured and tested for clonogenic survival, invasion inhibition and tumor spheroid growth model. The Akt-inhibitor MK-2206 and Temozolomide (TMZ) were added for different time treatments and in varying doses. Cultures were irradiated with single dose and fractionated γ-irradiation. Cellular modulation of Akt and p-Akt were assessed by Western blot analysis. MK-2206 reduced the expression of the phospho-Akt key protein in the PI3Kinase-Akt pathway, decreased cell survival, and inhibited migration, invasion and proliferation. MK-2206 enhanced the effects of radiotherapy (RT), presenting a radiosensitizing effect on MK-2206, additive in terms of cell survival, and synergistic in terms of inhibition of invasion, migration and growth. The radioenhancing effect of MK-2206 was most striking in inhibition of spheroid growth by fractionated RT; the radiosensitizing effect of MK-2206 was stronger than that of TMZ; no further radiosensitization was observed after combination of RT with both MK-2206 and TMZ. MK-2206 enhanced the in vitro effects of RT and TMZ in terms of decreased cell survival, invasion, migration and proliferation in malignant glioma. Effects could be ascribed to inhibition of Akt phosphorylation.

P.127. BEVACIZUMAB PLUS IRINOTECAN IN RECURRENT GLIOBLASTOMA MULTIFORME - EXPERIENCE IN THE JUAN RAMON JIMENEZ HOSPITAL

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PURPOSE: The prognosis for patients with recurrent glioblastoma multiforme is poor, with a median survival of 3 to 6 months. We present our experience in 5 patients treated with bevacizumab in combination with irinotecan. Primary endpoints: Efficacy of bevacizumab in combination with CPT-11 (irinotecan) in the treatment of patients with recurrent GBM by Progression-free survival, Objective response rate. Secondary endpoints: Overall Survival, duration of response, safety of treatment. PATIENTS AND METHODS: In this short study we treat patients with recurrent glioblastoma multiforme after surgery plus temozolamide and radiotherapy. temozolomide in combination with radiation therapy followed by 6 months of temozolomide has become the standard of care for newly diagnosed GBM. The five patients, received bevacizumab at 10 mg/kg plus irinotecan every 2 weeks. Each 4 cycles evaluated with MRI imaging. the mean age of patients was 48 years. 4 males and 1 female. The mean time since diagnosis of GBM to the start of radiotherapy and chemotherapy was 3 months. The mean cycles of CPT 11 BV was 19 (4-36). RESULTS: The median survival was 9.2 months. The progression-free survival from diagnosis to recurrence was 22 months. The mean dose of corticosteroids used for treatment of relapse was 4 to 8 mg/day. None of five patients developed relevanted-toxicity like CNS hemorrhage, thromboembolic complications (deep venous thrombosis and/or pulmonary emboli), fatigue, neutropenia or sepsis. One of the patients this study maintains complete response, one stable disease and three are in progression of the disease (1 died). CONCLUSION: Bevacizumab and irinotecan is an effective treatment for recurrent glioblastoma multiforme and has moderate toxicity, it is well tolerated. Our series of patients is small due a low incidence of GBM diagnosis in small hospitals like ours.

P.128. MIGRATORY CAPACITY OF BRAIN TUMOR INITIATING CELLS: A MOLECULAR AND CELLULAR DISSECTION OF TUMOR INITIATING CELLS IN HIGH-GRADE GLIOMAS

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RESEARCH GOAL: Glioblastomas (GBM) represent one of the most devastating human tumor forms. According to recent publications, the pathogenesis of these tumors may be based on the function of **B**rain **T**umor **I**nitiating **C**ells (BTIC). Therefore, it is relevant to investigate the transdifferentiation and migration potential of these cells through the identification of mechanisms controlling the generation of BTICs. This can be approached by the description of functional differences between **N**eural **P**rogenitor **C**ells (NPC), BTICs and **T**umor **C**ells (TC) in respect of migration in *in vitro*, *in situ* and *in vivo* assays, by investigating migrated cells by microarray analysis of microdissected cells, and by challenging the hypothesis that BTICs and TCs are able to re-differentiate into NPCs after si/shRNA transfection with the transdifferentiation-modulating transcription factors STAT3 and C/EBPß. METHODS: The following aspects are investigated: (1) functional and molecular differences between NPCs, BTICs and TCs are dissected by migration assays using live cell imaging for wound healing, spheroid assays and Boyden Chamber assays; (2) migration and invasion of living cells are investigated using *in situ* organotypic brain slice cultures and (3) the hypothesis that BTICs and TCs are able to re-differentiate into NPCs is challenged after si/shRNA transfection with STAT3 and C/EBPß. RESULTS AND PERSPECTIVES: Up to now, organotypic brain slice culture migration and live cell migration (wound healing) assays with BTICs transfected with

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siRNA were established. Stable shRNA lentiviral transfected NPCs and BTICs overexpressing STAT3 and/or C/EBPß as well as BTICs with a knockdown of STAT3 and/or C/EBPß were generated for analysis in the migration assays. Further, all original and engineered cells were characterized for epithelial and mesenchymal markers correlating to their potential of migration. At the moment we are investigating stably transfected cells in our functional assays and will perform a search for new markers correlating to stemness in BTICs and NPCs by investigating migrated vs. not migrated cells through microarray analysis of microdissected cells harvested by laser capture microscopy (LCM). Newly identified targets will be either cloned, over-expressed or silenced using si/shRNA or vector based strategies and further characterized in order to manipulate the tumorigenicity of NPCs and BTICs. Engineered cells will be inoculated in a nude mouse model to investigate their invasion potential in comparison to control cells.

P.129. BEVACIZUMAB IN COMBINATION WITH FOTEMUSTINE AS SALVAGE THERAPY IN RECURRENT ANAPLASTIC GLIOMAS: A PHASE II TRIAL

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BACKGROUND: The role of bevacizumab in the treatment of anaplastic gliomas is still unclear. The available data derive from retrospective and few prospective studies that reported response rates of 64%-67%, median progression-free survival (PFS) of 3-8 months, and median overall survival (OS) of 8-12 months. We report the preliminary results of a phase II study on patients with recurrent grade III gliomas treated with bevacizumab (BEV) in combination with fotemustine (FTM). PATIENTS AND METHODS: Patients with histologically proven anaplastic glioma, recurrent after standard therapy, were eligible. Treatment consisted of BEV at 10 mg/kg on day 1, 15 and FTM at 75 mg/m2/die on day 1, 8 and, after 3 weeks interval, followed by BEV at 10 mg/kg and FTM at 75mg/m2 every 3 weeks as a maintenance treatment, until tumor progression or unacceptable toxicity. MRI was performed at baseline, after 6 weeks from the start of therapy, and thereafter every 2 months. Response on MRI was defined according to RANO criteria as a reduction of enhancement on T1-weighted images associated with stability or reduction on FLAIR-images in patients with stable or decreasing dose of corticosteroids. RESULTS: Thirty-six patients (27 males and 9 females) were accrued and treated between May 2008 and September 2011. The majority of patients (22/36, 61%) had oligodendroglial tumors: 12 anaplastic oligodendrogliomas (O III) and 10 anaplastic oligoastrocytomas (OA III). 14/36 (39%) patients had anaplastic astrocytomas. The median age was 46 years (range: 29-66), median KPS was 90% (range: 60-100). Nine patients (25%) had received prior chemotherapy regimens (5 patients PC, 3 PC and dose-dense temozolomide, 1 PC and high dose tamoxifen and 13 patients were treated after reoperation (median of 2 surgeries, range: 2-4). At study entry 26/36 (72%) of patients were on steroids, with a median dosage of 4mg (range: 1-16). Median OS was 8.5 months (range: 4-45+) and OS-6 and OS-12 were respectively 75% and 33%. Median PFS was 5.1 months (range: 1-45+), and PFS-6 and PFS-12 were 39% and 14% respectively. The overall response rate was 47% (11% CR, 11% majorPR, 25% PR) with 47% of SD and 6% of PD. Steroids were reduced or stopped in 77% of patients. The most frequent side effects were: fatigue (61%), proteinuria (33%), arterial hypertension (30%), thrombotic events (19%), haemorrhagic events (11%), haematological grade 3-4 toxicity (8%). CONCLUSIONS: The combination of BEV and FTM in recurrent grade III gliomas after standard treatment seems to have some activity. Correlation with 1p/19q, MGMT methylation status and IDH1 and 2 mutations are ongoing.

P.130. BIMODAL ANTI-GLIOMA MECHANISMS OF CILENGITIDE DEMONSTRATED BY NOVEL INVASIVE GLIOMA MODELS

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BACKGROUND: Integrins are expressed in tumor cells and tumor endothelial cells, and likely play important roles in glioma angiogenesis and invasion. OBJECTIVE: We investigated the anti-glioma mechanisms of cilengitide (EMD121974), an $\alpha v\beta 3$ integrin inhibitor, utilizing the novel invasive glioma models, J3T-1and J3T-2. METHODS AND RESULTS: Immunohistochemical staining of cells in culture and brain tumors in rats revealed positive $\alpha v\beta 3$ integrin expression in J3T-2 cells and tumor endothelial cells, but not in J3T-1 cells. Established J3T-1 and J3T-2 orthotopic gliomas in athymic rats were treated with cilengitide or solvent. J3T-1 gliomas showed perivascular tumor cluster formation and angiogenesis, while J3T-2 gliomas showed diffuse single-cell infiltration without obvious angiogenesis. Cilengitide treatment resulted in a significantly decreased diameter of the J3T-1 tumor vessel clusters and its core vessels when compared with controls, while an anti-invasive effect was shown in the J3T-2 glioma with a significant reduction of diffuse cell infiltration around the tumor center. The survival of cilengitide-treated mice harboring J3T-1 tumors was significantly longer than that of control animals (median survival; 57.5 days and 31.8 days, respectively, $P < 0.005$), while cilengitide had no effect on the survival of mice with J3T-2 tumors (median survival; 48.9 days and 48.5, $P = 0.69$). CONCLUSION: Our results indicate that cilengitide exerts a phenotypic anti-tumor effect by inhibiting angiogenesis and glioma cell invasion. These two mechanisms are clearly shown by the experimental treatment of two different animal invasive glioma models.

P.131. DOES THE SPATIAL RELATIONSHIP OF PRIMARY GLIOBLASTOMA TO THE SUBVENTRICULAR ZONE IMPACT ON NEURAL STEM CELL MARKER EXPRESSION AND SURVIVAL?

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OBJECTIVE: There is an ongoing debate whether neural stem cells residing in the subventricular zone (SVZ), the predominant neurogenic region of the adult brain, give rise to glioblastomas (GBM). A recent publication demonstrated that the spatial relationship of GBM to the SVZ predicts a multifocal and invasive phenotype. We therefore sought to determine whether vicinity to SVZ impacts on neural stem cell marker expression and survival in patients with primary GBM. METHODS: Cryostate tissue sections of 106 primary GBM patients and 16 corresponding recurrent tumours were stained for six major neural stem cell markers (CD133, ALDH1A, GFAP delta, FABP7, SOX-2, SSEA-1). After digitalization of slides, quantification of expression was carried out using colour deconvolution. Respective preoperative MRI scans were reviewed and tumours were classified as follows: (I) GBM contacting SVZ and infiltrating cortex, (Il) GBM contacting SVZ but not involving cortex, (III) GBM not contacting SVZ but infiltrating cortex, (IV) GBM neither contacting SVZ nor infiltrating cortex. Clinical data were available for all patients analyzed. RESULTS: GBM localisation was mainly assigned to groups I (31.1%) and III (38.7%) and multifocal tumour growth was restricted to these two groups. Analysis of the whole patient sample failed to demonstrate a correlation between GBM localisation and patient survival; however, analyzing the subgroup of completely resected patients (30.2%), a significant survival benefit (OS: $p = 0.04$; PFS: $p = 0.03$) was seen for GBMs contacting the SVZ (I, II). Noteworthy, in tumours adjacent to the SVZ (I, II), a significant correlation to stem cell marker expression was only found for CD133 ($p = 0.006$) whereas GBMs with subcortical localisation (II, IV) demonstrated a significant overexpression of FABP7 ($p = 0.03$). Interestingly, 53-87% of the recurrent tumour tissues analyzed displayed enhanced stem cell marker expression compared to the respective primary tumours. CONCLUSION: These preliminary findings mitigate the hypothesis that GBMs contacting the SVZ are enriched in (potentially tumourigenic) neural stem cells that impact on patient survival. However, in these tumours a complete resection seems to exert an exceptionally prognostic benefit. Multivariate analysis is currently under way to underline the results.

P.132. EXPERIENCE ON THE USE OF CHRONIC ORAL TAMOXIFEN WITH TEMOZOLOMIDE RECHALLENGE AS A SECOND LINE TREATMENT OF GBM RECURRENCE: A SINGLE CENTRE EXPERIENCE

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INTRODUCTION: Several multidisciplinary approaches have been developed for the therapeutical management of glioblastoma multiforme (GBM). First line treatment consists of surgical exeresis followed by concomitant

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radiotherapy and chemotherapy, according to Stupp et al. Second line treatment is not well defined, thus being often personalized, based on radiological findings (tumor response on brain-MRI). OBJECTIVES AND METHODS: In this study, we propose the routinary use of Tamoxifen (TAM) in association with Temozolomide (TMZ) dose-dense schedule as a second line treatment for recurrent GBM. We selected a small court of 32 patients on 100 consecutive cases treated at our Institution since 2007, who completed the concomitant phase of the Stupp's protocol and at least the first adjuvant treatment cycles. Dose-dense TMZ and continuos daily oral TAM were administered to this court of patients. The court of patients was selected considering the single patient's compliance, TMZ first line response, KPS and previous tromboembolic events. TAM administration was suspended in case of multifocal tumor recurrence, introducing Fotoemustine as a third line treatment. We didn't use surgical exeresis as a choice factor. Antiplatelet drugs were administered to all patients in order to prevent tromboembolic events. RESULTS: 16 patients underwent gross total resection, 5 underwent subtotal resection and 11 underwent partial resection. Median age was 58 y-o., median KPS was 80. Selecting patients according to KPS, treatment compliance and TMZ response, an increased average and median overall survival (MOS) were noticed. After TMZ plus TAM, median time tumor progression (TTP) was 10 months. MOS was 18 months. Moreover, we observed no toxic reactions to TAM; while intolerance to this treatment (such as mood's alterations) was reported in 1 patient. Multifocal relapse after a long period treatment occurred in 3 patients. CONCLUSIONS: Based on our experience, a modification of dose-dense TMZ schedule, introducing TAM as a well tolerated add-on molecule, is a valid and safe second line treatment for recurrent GBM, increasing median OS and prolonging TTP. Our schedule consists of one week on - one week off TMZ (60-70 mg/m2) rechallenge plus TAM (100 mg/day on average) in patients responding to TMZ. This approach allows a longer treatment with TMZ, maximazing the benefits of a prolonged use of this molecule and contemporary reducing the disease's progression.

P.133. BEVACIZUMAB FOR RECURRENT GLIOBLASTOMA, EARLY OBSERVATIONS ON PATIENT OUTCOME IN THE BELGIAN MEDICAL NEED PROGRAM

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Bevacizumab (BEV), a monoclonal antibody targeted against the vascular endothelial growth factor is a potent inhibitor of tumor related neoangiogenesis and has demonstrated anti-tumor activity in patients. with glioblastoma who experience a recurrence following prior therapy with surgery, radiation therapy and alkylating chemotherapy. Based on evidence from uncontrolled phase II clinical trials, BEV was registered in this indication in the US but not in the EU. Given the unmet need for active therapeutic options in glioblastoma, patients who experience a recurrence of their disease, a medical need program was initiated by the Belgian competent authorities, allowing the use BEV for this patient population in 14 neuro-oncology centers who had prior experience with the use of anti-angiogenic therapies. During the first year of this program (Nov 2010 to Dec 2011) a total of 143 patients were enrolled in 14 centers (median no. of patients per center: 8, range 3-22). Baseline patient characteristics: 61% male and 39% female; median age 56y (range 16-82); ethnicity: 92% Caucasian, 6% Arabic/North-African; 2% other; 57% of patients had undergone more than one neurosurgical resection; all patients had failed radiation therapy and temozolomide, and 55% of patients had failed at least one prior therapy for recurrent disease (e.g. therapeutic vaccination, lomustine, PCV); baseline WHO-performance-status 0/1/2/3: respectively 7, 70, 18 and 5%; corticosteroid use 68% of patients. At the time of this analysis (2 February 2012), bevacizumab treatment was ongoing in 36 patients. On average 7 bi-weekly administrations (at a dose of 10 mg/kg) were administered per patient (range 1 to 41+). Treatment was stopped in 86% of patients because of progression of disease, and in 5,6% because of adverse-events. There were 5 grade 4 adverse-events, none considered related to bevacizumab, and 27 grade 3 and 59 grade 2 adverse-events of which thrombo-embolism (2pts grade 2, 1pt grade 2) and thrombocytopenia (3pts grade 2, 2pts grade3) were most frequent and considered BEV related. The best objective tumor response according to RANO criteria (investigator assessment, available for 96 patients) included: 4 CR (4,2%), 29 PR (30,1%), 35 SD (36,5%), and 28 PD (29,2%); for a BORR of 34% and a DCR of 70%. The median PFS was 12 weeks (95% CI 10-13), and the 6-months PFS-rate 15% (95% CI 12-17). The median OS was 26 wks (19-30) and 6-months OS-rate 50% (95% CI 39-61). We conclude that not withstanding the less favorable survival observed for our more heavily pretreated patient population, BEV was well tolerated and resulted in an objective tumor response rate that seems comparable to the results reported in prospective studies. Our observations therefore legitimate the availability of BEV in this MNP in the absence of alternative treatment options or access to clinical trials for this poor prognosis patient population.

P.134. A RETROSPECTIVE STUDY OF SUSTAINED ADMINISTRATION VERSUS THE STANDARD 6 CYCLES OF ADJUVANT TEMOZOLOMIDE AFTER CONCOMITANT RADIOCHEMOTHERAPY FOR PATIENTS WITH GLIOBLASTOMA

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BACKGROUND: Glioblastoma is the most common primary malignant brain tumour in adult patients. It has a very poor prognosis despite surgery, radiation therapy and chemotherapy. Radiation therapy with concomitant temozolomide followed by six cycles of adjuvant temozolomide is currently the standard treatment after surgical resection or biopsy in patients with a good performance status. In the EORTC 26981/22981-NCIC CE3 phase III trial temozolomide was stopped after six cycles based on an arbitrary decision, but the optimal duration of adjuvant temozolomide remains uncertain. To date there is very few data investigating additional cycles of temozolomide in terms of efficiency and toxicity. However some physicians propose treatment maintenance to their patients when they are stable after the sixth cycle. Materials and methods. We conducted an observational retrospective study of WHO grade IV glioma patients diagnosed between 2007 and 2010 in two French centers (Nancy and Dijon). Patients were considered stable after six cycles of adjuvant temozolomide and underwent either follow-up or additional adjuvant temozolomide afterwards. We compared the two groups in terms of overall survival, progression-free survival and toxicity. RESULTS: The clinical files of 448 patients were reviewed in both centres. A total of 59 patients was included. Among them were 21 women and 38 men. Mean age at diagnosis was 55,2. Mean Karnofsky performance scale index (KPS) at diagnosis was 74,3. Pathological examination found 58 glioblastomas and one gliosarcoma. Surgery consisted of resection for 49 patients and biopsy for the other ten. All patients received radiation therapy with concomitant temozolomide. 38 patients received six cycles of adjuvant temozolomide and were then followed up. 21 patients received nine or more cycles of adjuvant temozolomide. In this group the mean total adjuvant cycles was 14,5 (9-26). Statistical analysis in terms of overall survival and progression-free survival is on-going. There was no grade 3 or 4 toxicity observed in patients for whom temozolomide was maintained after 6 cycles. CONCLUSION: To date there is very few data investigating the efficiency and toxicity of additional cycles of temozolomide after radiochemotherapy for patients with WHO grade IV glioma patients. As suggested in recent studies, we observed no increase in toxicity with prolonged duration of treatment. Prospective studies are necessary to assess a potential benefit of this strategy in terms of overall survival and progression-free survival.

P.135. BEVACIZUMAB PLUS FOTEMUSTINE COMBINATION: ACTIVITY AND SAFETY IN RECURRENT MALIGNANT GLIOMAS

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BACKGROUND/PURPOSE: Recurrent malignant gliomas (RMGs) have a dismal prognosis with a median survival of 4-6 months. Although bevacizumab (BV) has been showed to provide encouraging tumor responses and prolonged survival in the treatment of RMGs no clearly established chemotherapy (CT) regimens do exist. We performed a prospective study to evaluate the activity and the toxicity of BV in combination with fotemustine (FTM) in RMGs. METHODS: We conducted a phase II study in adults with RMGs. Patients (pts) with the presence of other condition that would have made the treatment unsafe were excluded. Enrolled patients received BV intravenously (iv) at the dose of 10 mg/kg every 2 weeks (induction

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phase) and then at the dose of 15 mg/kg every three weeks in the maintenance phase. FTM was administered iv weekly for 3 consecutive cycles at 60mg/m2 (induction phase) followed by triweekly cycles at 75 mg/m2 (maintenance phase) given after 5-week rest period. MGMT gene promoter methylation status was evaluated. RESULTS: Twenty-three pts (14 M, 9 F, (median age 42.5 yrs [25 - 68], median KPS 80 (70 - 100) were enrolled. Fifty-six percent of patients had received only one previous line of CT, namely temozolomide given in association with radiotherapy; 44% of pts were treated with two prior lines of CT. Response rate was 26% (all partial responses). Seven patients (30.4%) achieved disease stabilization (disease control rate: 56.4%) and 39% (9/23) pts had a clinical benefit. Responses were observed in all histotypes. Median PFS and OS were 4 months (95% C.I.: 2.5-5.5) and 6 months (95% C.I.: 5.2-6.7), respectively. Overall survival differed with regard to response: 8 months (95% C.I.: 5.1-10.9) for pts with partial response; 6 months (95% C.I.: 4.7-7.3) for non-responders; 3 months (95% C.I.: 1.4-4.5) for pts with progressive disease. MGMT status was evaluated in 16 pts (69.5%). We observed 10 pts without MGMT methylation (43.5%) and 6 pts with MGMT methylation (26%). Pts with MGMT methylation achieved 33% of response while non-methylated MGMT pts had 10% of response. The most common toxicities (all grades) were neutropenia (21.7%), thrombocitopenia (13%), hypertransaminasemia (8.6%). Grade 4 adverse events (AEs) were neutropenia (1 pts, 4.3%) and lymphocitopenia (1 pts, 4.3%). AEs related to BV included venous thromboembolism (2 pts, 8.7%), 1 asymptomatic central nervous system hemorrhage (4.3%), proteinuria (2 pts, 8.7%) and a grade 2 gastrointestinal perforation. CONCLUSION: The combination of BV and FTM in RMGs revealed a good activity in pts previously treated with CT. Treatment was well tolerated.

P.136. IS ANGIOGENESIS AN EFFICIENT TARGET FOR THE TREATMENT OF GLIOBLASTOMA MULTIFORME

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INTRODUCTION: Malignant gliomas are the most common primary tumors of the cerebrospinal axis. Despite the combination of various treatments including surgery, radiotherapy and chemotherapy, patients diagnosed with GM have a poor prognosis. Postoperatively, temozolomide (TMZ) concomitant and adjuvant to radiation oncology treatment is considered to be the standard of care for patients with high-grade CNS malignant gliomas. The failure of existing treatments for malignant gliomas has been attributed to the existence of cancer stem cells and their chemoresistant properties, as well as their ability to stimulate neoangiogenesis. Material and methods. In the study 21 patients were included who underwent brain tumor resection. We aimed to obtain primary cultures of biopsies intraoperatively and isolation of tumor stem cells for MTT testing chemosensitivity to temozolomide (TMZ), but also the influence of TMZ association with Metformin (MET) and 2-methoxiestradiol(2-ME). Apoptosis, cell cycle and autophagy was performed to asses the tumor stem cells response to chemotherapeutics. In parallel, tumor fragments as explants were tested for ability to induce spontaneous neoangiogenesis in vitro, by developing a 3D model of angiogenesis in fibrin gel. Isolated cancer stem cells were also cultivated in fibrin gel in a capillary tube formation assay, in comparison with endothelial cells (HUVEC cells to study the influence of TMZ therapy and factors inhibitors of angiogenesis (bevacizumab, sorafenib and thalidomide) on tumor vasculature development. RESULTS: 60% of the tumors tested in vitro for sensitivity to TMZ, responded to the drug. Isolated tumor stem cells had an increased proliferation rate to treatment with TMZ. Resistance to TMZ, in some cases was converted with Metformin and 2-methoxiestradiol. Sorafenib association with MET and 2-ME induced autophagy response. In 11 cases of 19, TMZ treatment induced or augmented angiogenesis process. Glioblastoma cells and isolated tumor stem cells developed spontaneously in fibrin gels capillary tubules, known to be specific to endothelial cells. CONCLUSIONS: Tumor stem cells selected by treatment with TMZ (which are resistant to chemotherapy) under the influence of vascular niche factors (VEGF, stromal derived factor 1, PDGF) will differentiate into endothelial cells of tumor vasculature development. New alternative chemotherapeutic tools with less toxicity are considered in our study such as Metformin and 2-methoxiestradiol in association with TMZ.

P.137. HIGH GRADE GLIOMAS - THE ROLE OF MAXIMAL CYTOREDUCTIVE SURGERY

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INTRODUCTION: High grade gliomas are aggressive cancers. Despite advances in surgical techniques, and improvement in radiation treatment and chemotherapy, the median survival of these patients has changed little over the last decades. The purpose of this study is to add some arguments in favor of surgery and especially of the radical surgery in malignant gliomas. Material and methods. This is a retrospective study of a single surgeon, single centre and is based 540 cases of high grade cerebral gliomas operated between 01.01.2000-31.12.2011 at the Department of Neurosurgery. Total removal was the goal in all the cases. We analyzed age, gender, type and duration of symptoms, type of surgery, pathological diagnosis and the correlation of these factors with overall survival. RESULTS: The results show according to their histological features, the following dispersions: anaplastic astrocitomas (26%), glioblastoma multiforme (66%), high grade oligodendrogliomas (5%) and high grade ependimomas (3%). Age ranged from 6 to 82. The interval between the debut of symptoms and admission in the hospital was one month for almost half of the cases. From a clinical point of view increased intracranial pressure (ICP) (78%) was the major sign followed by focal weakness, seizures (18.9%), and aphasia (11.5%) Gross total removal of the tumor was achieved in the majority of the cases (> 80%). The age and type of surgery are prognostic factors that significantly influenced the survival at 12, 18 and 24 months. CONCLUSION: Glioblastoma multiforme is the most frequent type of an operated glioma. The most important factor for a good outcome of the surgical treatment is the extent of resection. Our study provides a new argument in favour of gross total removal. Despite advances in multimodal treatment, the overall prognosis remains poor.

P.138. CYTOMEGALOVIRUS INFECTION OF PRIMARY GLIOBLASTOMA CELLS INDUCES STEMNESS THROUGH A NOTCH-DEPENDENT PATHWAY

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Glioblastoma multiforme (GBM) is the most common primary intracranial tumor in adults and is associated with poor prognosis despite aggressive surgical and chemoradiotherapy. Previous work from our group showed that 99% of GBM tumors are infected with Cytomegalovirus (CMV) and that the infection level is a prognostic factor for patient survival. CD133 is considered to be a putative marker of cancer stem cells (CSC) in many different tumors, including glioblastoma. CSC is a population of cells, which is believed to have an ability to survive multiple oncological therapies and give raise to tumor recurrences. Given the critical role of CSC in tumor initiation, progression and recurrence, we further investigated the ability of CMV to induce a CSC phenotype in primary GBM cell lines. We detected CMV Immediate Early (IE) protein expression in 21 of 22 primary GBM tumors by flow cytometry, these GBM tumors exhibited diverse CD133 positivity (1-70%). We found that the grade of CMV infection in Cancer Stem Cells obtained from primary glioblastoma tumors was a prognostic factor for patient survival (P value 0.0271). In vitro, we found that CMV infection induced CD133 expression and neurosphere formation and non-adherent growth in primary GBM cell cultures, which otherwise grow adherently. CMV infection also specifically induced expression of the transcription factor Notch-1 that is critical for stem cell maintenance, but not Nestin, SOX-2, BMI-1 and Oct-4. Interestingly, treatment of CMV infected primary GBM cell lines with Gamma Secretase inhibitor (GSI) that targets the Notch signaling pathway or the antiviral drug Ganciclovir blocked neurosphere formation indicating a critical importance of CMV infection and Notch signaling in this process. These data suggest that the Notch signaling pathway may be a possible therapeutic target for the treatment of GBM, in combination with antiviral therapy.

P.139. EFFECTS OF VALGANCYCLOVIR AS AN ADD-ON THERAPY IN PATIENTS WITH CYTOMEGALOVIRUS-POSITIVE GLIOBLASTOMA: A RANDOMISED, DOUBLE-BLIND, PROOF-OF-CONCEPT STUDY

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PURPOSE: Cytomegalovirus (CMV) is highly prevalent in glioblastomas, and anti-CMV therapy efficiently inhibits the growth of CMV-positive brain

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tumours in vivo. In 2006, we initiated a randomized, double-blind, placebo-controlled, proof-of-concept study to examine the safety and efficacy of valgancyclovir as an add-on therapy in glioblastoma patients. PATIENTS AND METHODS: Forty-two glioblastoma patients were randomized in double-blind fashion to receive valgancyclovir or placebo in addition to standard therapy for 6 months. Thereafter, valgancyclovir could be prescribed. PRIMARY ENDPOINT: Magnetic resonance images were obtained before, after and 3 and 6 months after surgery to evaluate treatment efficacy by measuring contrast enhancing tumour volume. Survival data were analysed for study patients and for historical controls in explorative analyses. RESULTS: Trends but no statistically significant differences were observed in tumour volumes in valgancyclovir and placebo patients at 3 (3.58 vs 3.31 cm^3, $P = .2881$) and 6 (7.44 vs 13.75 cm^3, $P = .2120$) months, respectively. Median overall survival (OS) was similar in both groups. However, OS was 24.2 months (95% CI, 17.4 to 40.3) in patients who received at least 6 months of valgancyclovir (Val > 6M), 13.1 months (95% CI, 7.9 to 17.7, $P<.0001$) in patients receiving short or no valgancylovir treatment, and 13.7 months (95% CI, 6.9 to 17.3, $P = .0015$) in historical controls. OS at 4 years was 27.3% in Val > 6M patients versus 5.9% in historical controls ($P = .0466$). CONCLUSION: Due to unexpectedly high OS in this study, further investigation to evaluate whether CMV targeted therapies can improve outcome in glioblastoma patients are under way.

P.140. IMPROVED SURVIVAL OF GLIOBLASTOMA PATIENTS IN THE MODERN ERA: FIRST RESULTS FROM A MULTICENTER PROSPECTIVE REGISTRY - THE PROJECT OF THE EMILIA-ROMAGNA REGION IN NEURO-ONCOLOGY (PERNO)

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BACKGROUND: The role of temozolomide (TMZ) concurrent with and adjuvant to radiotherapy (RT) in the treatment of glioblastoma (GBM) has been demonstrated by the EORTC 22981/26981-NCIC CE.3 (EORTC/NCIC) randomized trial, and has been widely accepted as the standard treatment. The impact of RT/TMZ in the general patient population was assessed in the context of the Registry of the Project of Emilia-Romagna Region in Neuro-Oncology (PERNO), that represents the first italian prospectic observational population-based study in neuro-oncology. METHODS: Approvals from local Ethical Committees were obtained by 8 participating centers. Patients (pts) who met the following inclusion criteria were evaluated: age $\geq$18 years; PS 0-3; histologically confirmed GBM, no previous or concomitant non glial tumoral disease, resident in Emilia Romagna region. The data were prospectively collected. RESULTS: From January 2009 to January 2011, 194 GBM pts were enrolled. The median age was 62.5, with 26% of pts over 70 years. After surgery pts received RT/TMZ (73%), RT alone (19%), TMZ alone (5%) or no further treatment (3%); 22% were included in clinical trials. Median overall survival (OS) was 12.9 months. Pts <70 years received RT/TMZ in 85% of cases. In this group of pts mOS was 17 months (95%CI: 15.4-18.6). Interestingly, pts <70 years included in experimental clinical trials showed a significant OS improvement ($p = 0.04$). In multivariate analysis, only extent of surgery ($p = 0.047$), KPS ($p = 0.01$) and RT/TMZ ($p < 0.001$) were associated with OS in pts <70 years. CONCLUSIONS: Our population data reproduces the beneficial effect of RT/TMZ from the EORTC/NCIC randomized trial, confirming how this successful approach as been widely incorporated in daily practice. Interestingly, our data suggest that the survival of GBM pts treated with RT/TMZ could be greater than patients treated with RT/TMZ in the EORTC/NCIC trial at the beginning of this century.

P.141. RADIOSENSITIZING EFFECTS OF HDAC INHIBITORS AND RESPONSE PROFILING IN PATIENT-DERIVED GLIOBLASTOMA CULTURES

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Introduction Histone deacetylase inhibitors (HDACi) are potent radiosensitizers and have gained increasing attention in glioblastoma (GBM) research. We compared the radiosensitization of HDACi in serum-free patient-derived GBM cultures. We focussed on aspects relevant for the translation of HDACi to the clinical setting: timing, radiation (RTX) fractioning and differences in molecular profiles. Methods GBM cultures were prepared from fresh tumor material. Vorinostat (SAHA), valproic acid (VPA), Scriptaid, panobinostat and entinostat, and RTX were selected for the experimental treatment on the cell cultures. Viability and cell confluence were measured for treatments. Treatment response was related to GBM clusters using RNA expression. Acetylated histone H3, MGMT, p21Cip1/WAF1, Bcl-2, PTEN, LC3B and caspase-8 protein levels were blotted. Altered DNA damage was assessed by γH2AX, and apoptosis by caspase-3/7 activity. Results Pre-incubation of cells with HDACi 24h prior to RTX resulted in up to 40% additional viability decrease. Radiosensitization was observed in 71% (SAHA), 47% (Scriptaid), 47% (VPA), 58% (panobinostat) and 53% (entinostat) of cultures ($n = 18$). Fractioning the RTX resulted in similar radiosensitization as single dose. Comparing a responder (R) and non-responder (NR) revealed hyperacetylated H3 predominantly in the first compared to the latter. SAHA lowered MGMT levels in the responder in mono and combination therapy. In case of the other HDACi and in the non-responder, MGMT was upregulated. p21Cip1/WAF1 was upregulated in the non-responder and downregulated in the responder. Bcl-2 was upregulated by Scriptaid, entinostat and panobinostat (NR). PTEN was by most treatments downregulated, and upregulated by panobinostat (NR). Caspase-3/7 but not caspase 8 levels correlated with response rates. LC3B conversion was observed only in the responder. Increased γH2AX foci by all HDACi except entinostat were observed (R). In the non-responder, only SAHA/RT slightly induced γH2AX. Subtyping based on RNA expression profiling (Verhaak, Gravendeel) did not predict HDACi response, but supervised cluster analysis showed separate clustering between responders and non-responders for SAHA. Conclusion HDACi as monotherapy and radiosensitizer exert differential effects in different serum-free GBM cultures. SAHA and panobinostat seem the most potent radiosensitizers based on percentage responders. Pre-incubation with HDACi 24h prior to RTX results in better radiosensitization than administration post-RTX. Fractioning does not eliminate radiosensitization. Commonly used GBM RNA based cluster profiling did not predict response to HDACi treatment, however, we found specific RNA profiles in supervised cluster analysis in the case of SAHA treatment.

P.142. IS THERE A ROLE FOR ANTI-CMV THERAPY IN GLIOBLASTOMA? -THE TALE OF VALGANCICLOVIR AS ADD-ON TO STANDARD SURGERY AND RADIOCHEMOTHERAPY

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PURPOSE: Cytomegalovirus (CMV) is highly prevalent in glioblastomas, and anti-CMV therapy efficiently inhibits the growth of CMV-positive brain tumours in vivo. Here, we aimed to retrospectively evaluate the survival of glioblastoma patients who have received Valganciclovir treatment as add on therapy at the Karolinska University hospital, Stockholm Sweden. PATIENTS AND METHODS: Since 2006, thirty-seven glioblastoma patients receiving standard radiochemotherapy after surgical removal of >90% of contrast enhancing tumor (except one patient with callosal tumor who had 60% tumor removal) have been treated with valganciclovir as add-on therapy. 23 of these were included in a randomised, double-blind, placebo-controlled, proof-of-concept study to examine the safety and efficacy of valganciclovir as an add-on therapy in glioblastoma patients. Additionally, 14 patients were prescribed valganciclovir for compassionate use according to the same protocol. All patients received oral valganciclovir treatment for at least 6 months, up to 5 years. Overall survival (OS), and Time to tumour progression (TTP) data were analysed for study patients and was compared to consecutive historical control patients with the same inclusion criteria collected during 2006-2008 ($n = 85$). All statistical hypotheses were two-sided log-rank test using a significance level of 5%. RESULTS: The median OS for patients receiving >= 6 months of Valganciclovir treatment was 29.2 months (95% CI, 21.2 months, upper limit not reached) vs 15.1 months (95% CI, 11.3 to 17.1 months, $p <0.0001$) in historical controls. The 2 year survival for the treated cohort was 65.7% vs 16.5% for controls ($p <0.0001$). Patients receiving continuous valganciclovir treatment showed improved survival: the median estimated OS was 40.3 months ($p <0.0001$), and 79.2% were alive at 2 years; patients who interrupted valganciclovir treatment at 6 months had OS of 17.4 months ($p = 0.78$) compared to controls, respectively. There were no severe side effects of this antiviral therapy; all patients could receive chemotherapy in addition to valganciclovir treatment. CONCLUSION: The unexpectedly high OS in glioblastoma patients receiving continuous valganciclovir therapy warrants further investigation to confirm whether CMV targeted therapies can improve the outcome in glioblastoma patients.

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P.143. IDENTIFICATION OF PROGNOSTIC FACTORS IN A NON-SELECTED POPULATION OF HIGH-GRADE GLIOMAS

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INTRODUCTION: High-grade gliomas (HGG) have a dismal prognosis despite aggressive treatment. To optimize the treatment algorithms it is of importance to identify patient-related prognostic factors. The purpose of this study was to identify prognostic factors in a complete population of adult patients with HGG in a pre-specified geographical area (Region of Southern Denmark) and in a pre-specified time period (1 January 2005- 31 December 2009). METHODS: Patients were identified using the Danish Cancer Registry and the National Pathology Data Bank. Survival was analyzed using the Kaplan-Meier survivor function and the prognostic values were estimated by the Cox proportional hazard model. RESULTS: The population identified comprised 355 patients of which 291 had histological confirmed HGG (233 with WHO grade 4 tumors, 58 with WHO grade 3 tumors) and 64 were diagnosed clinically based on the medical and radiological report. For the entire population ($n = 355$), the median overall survival (MS) was 7.7 months. For grade 3, grade 4, and the clinically diagnosed patients the MS were 10.2 months, 9.7 months, and 1.9 months, respectively. For the entire population no increase in MS was seen during the 5 year period. A trend towards improved MS was seen in patients younger than 60 years, increasing from 10.6% to 21.4% ($p = 0.07$). No increase in MS was seen in patients older than 60 years. In the multivariate analysis younger age, performance status (PS) 0-1, no neurologic deficits, tumors not crossing midline and receiving curative treatment were associated with a better prognosis. PS 0-1 was the strongest prognostic factor (HR 25.7, 95% CI 6.29-105.3, $p < 0.0001$), but the effect diminished with increasing age. A total of 162 patients (45.6%) had curative intended treatment including surgery, high-dose radiotherapy, and concomitant chemotherapy (grade 4 only). These patients had a prolonged survival as compared to patients receiving palliative treatment; MS 33.3% vs. 8.6% respectively ($p < 0.001$). Over time a significant increase in the proportion of patients having curative treatment was seen ($p = 0.006$). A sub-group consisting of 55 patients with grade 4 tumors had PS 0-1 and received curative intended treatment. These patients had a remarkable good prognosis with MS of 21.5 months, 43.6% survived more than 2 years. CONCLUSION: Patients who benefit substantially from post-surgical treatment can be identified by the clinical parameters such as PS 0-1, lack of neurologic deficit, and a tumor that does not cross the midline. Younger age is associated with better prognosis, but also older patients with a good prognostic profile benefit from post-surgical treatment. Although the number of patients, who receives curative intended treatment, is increasing, the group of elderly patients (> 60 years) offered no treatment or surgery alone is increasing as well thereby preventing an increase in OS.

P.144. EFFECT OF SINGLE FRACTIONED RADIATION THERAPY AND IMMUNOTHERAPY IN A RAT GLIOMA MODEL

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This study focuses upon the effect of radiotherapy (RT) in rats with implanted glioma tumours, with RT as single therapy or in combination with immunotherapy, as well as the non-target abscopal effect of RT. Cerebral glioma tumours were created by inoculating glioma cells stereotactically intracranially. The rats were treated with RT and immunization at day 7 after inoculation and immunization was repeated at up to two further occasions, at day 21 and 25. Subcutaneous inoculation of the rat glioma was performed in the right leg with 200 000 cells for the primary tumour, whilst 50 000 cells were inoculated into the left leg in order to simulate a secondary smaller tumour. *For intracerebrally* implanted N29 glioma tumour cells RT alone had no significant effect on the survival time. Immunization increased the survival time 60% ($p = 0.04$). Immunization combined with 5 Gy radiation therapy increased the survival time 87% ($p = 0.003$) with 75% complete remissions ($p = 0.03$), and with 15 Gy the survival time increased 45% ($p = 0.03$) with 63% complete remissions. *For subcutaneously* implanted N29 glioma tumors RT (20 Gy) was given only to the tumours located on the right leg. The difference of the tumour growth rate of the unirradiated left side as compared to unirradiated controls, defined as the abscopal effect, was significantly different from zero in the group of rats treated with RT only. Contrary to this, the abscopal effect for immunization alone or in combination with RT was not significantly different from zero. The finding that immunization combined with a single session of RT increased the survival time 87% as compared to the controls and lead to 75% complete remissions in an intracranial rat glioma model, might be of importance also in the clinical praxis. Due to the moderate absorbed dose, relapse patients previously treated with full dose RT might benefit from a single fraction radiation therapy of 6 Gy combined with immunotherapy. Another benefit of the moderate absorbed dose is that, if the response in not complete after the first treatment, additional combined treatments with single fraction RT and immunotherapy could be given at a few weeks interval.

P.145. GLIOBLASTOMA MULTIFORME: A MULTIVARIATE ANALYSES OF SINGLE INSTITUION DATA IN PATIENTS TREATED WITH RADIOTHERAPY IN ASSOCIATION WITH TEMOZOLOMIDE

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BACKGROUND AND AIM: Since the data published by Stupp et al in 2005 it has been the standard that patients diagnosed with primary Glioblastoma (GBM) in performance status 0-2 were treated with surgery followed by radiotherapy in association with concomitant and adjuvant temozolomide (RT/TMZ). We present the result of an unselected, prospective, consecutive cohort of GBM patients in a single institution with RT/TMZ from 2006 until ultimo 2010. The patient were treated after the same strategy and no patients were lost in follow up and the median observation time was 3.8 years (range: 0.7-6,6). Overall survival, progression free survival and response to treatment were used as endpoints and several clinical and paraclinical features were statistically analysed as indicators of prediction of survival and response. MATERIAL AND METHODS: Two-hundred and twenty seven patients have been included. The dataset includeded 147 men and 80 females. The median age was 59.5 years (range: 22.6-75.4). Data on overall survival were available for all patients. There was 185 patients registered as dead. Two hundred and eighteen patients had data on time to progression, of these 195 have registered with progression. STATISTICS: Univariate and multivariate analysis of response data are done using logistic regression analysis modelling the probability of MacDonald response at 3 and 6 months as well as the best response. Estimates of survival probabilities for overall survival (OS) and time to progression (TTP) have been done by the Kaplan-Meier method. Univariate and multivariable analysis of OS and TTP for the chosen explanatory variables have been done using the proportional hazards regression model (Cox). Analysis of time dependent variables have been done using the landmark method as well as the time dependent Cox regression model. P-values less than 5% are considered significant. Calculations have been done using SPSS (ref version?) and SAS (v9.2, SAS Institute, Cary, N.C.; USA). RESULTS AND CONCLUSION: Two year survival was 26 % and 5 year survival 9 %. The following parameters predicted influence of survival in multivariate analyses; age, performance status, steroid use at the time of RT/TMZ and reoperation. The following parameters did not predict survival; Gender, tumour multi focality; extent of primary surgery, size of tumour at the beginning of RT/TMZ, P53 and EGFR status. MGMT status was marginal correlated to survival. 20 patients had complete or partial response and response was correlated to extent of primary surgery, age and the combination of MGMT and P53 status. Based on the data we could construct an estimation of Best/worst case. The results showed a continuum. Best case was a patient 50 or less, performance status 0 not using steroid at the beginning of RT/TMZ with a median survival of 36 months as compared to a patient of 70 years or more, performance status 2 and steroid user with a median survival of 9 months.

P.146. MALIGNANT SPINAL CORD COMPRESSION IN CEREBRAL GLIOBLASTOMA MULTIFORME: A RETROSPECTIVE, MULTICENTRIC CASE SERIES

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Glioblastoma multiforme (GBM) is the most common malignant primary brain tumor in adults. Compared to other malignancies, remote metastases in GBM are rare. However, multicentric spreading within the central nervous system is common and also metastases to the spinal cord are reported. Some of these drop metastases may also lead to malignant spinal cord compression (MSCC). METHODS: We retrospectively identified 9 patients from 2001 to 2010, performed data analysis according to a standardized

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clinical protocol and. provide a review of the literature on this rare condition. RESULTS: MSCC from cerebral GBM is rare and was found in approximately 1 % of GBM patients. Median age of 54 years in this case series is comparable to GBM patients without MSCC. Treatment regimens for cerebral GBM and overall survival was similar to patients without MSCC. Spinal metastasis seems to occur in the advanced state of the disease,. and the outcome subsequently is extremely poor. All patients presented with multicentric radiological features of GBM on cerebral MRI when MSCC was diagnosed. Subependymal enhancement is another common radiological finding in GBM patients with spinal drop metastases. Steroids and focal radiotherapy were applied in all patients, with only little clinical benefit. *Interpretation:* The present study is the largest case series demonstrating multicentric cerebral distribution and subependymal enhancement of GBM on cerebral MRI at time of MSCC. According to our results, no specific treatment recommendations for MSCC in GBM patients can be given. However, accurate diagnosis of MSCC in GBM patients with spinal signs. and symptoms can lead to adequate symptomatic management and improvement of quality of life in terms of best palliative care.

P.147. THE COMPLEMENT SYSTEM AND THE GLIBLASTOMA MULTIFORME

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Components of the adaptive immune system have been identified in GBM patients, indicating involvement of immune activation in the pathology of GBM. Surprisingly, very little is known about the contribution of innate immunity in GBM patients. The human complement system forms a great constituent of the innate immunity comprising soluble and membrane-associated proteins. The activated complement system has the capability to promote carcinogenesis and facilitate the fundamental necessities of the malignant cell including; sustaining proliferative signaling, angiogenesis, resistance to apoptosis, modulating anti-tumor response and activating invasion and migration. So, potentially the activated complement cascade could exert great influence on progression and survival of tumor patients. Three pathways of complement activation have been recognized; the lectine pathway, the classical pathway and the alternative pathway. These pathways are activated via their recognition molecules, C1q, MBL and C3-H2O. Genetic variants, both common Single Nucleotide Polymorphisms and mutations have been identified in the complement genes. These SNP's could result into complete MBL deficiency with a frequency up to 30% in healthy Caucasian adults. Although being very rare, mutations in either one of the three genes encoding for C1q will lead C1q deficiency. We performed ELISA and IHC on sera and tissues derived from glial tumor patients versus healthy controls. Compared with sera derived from healthy blood donors, patients with GBM showed a significant decrease of C1q and a significant increase of MBL. C1q was highly present in tumor tissue, suggesting a secondary deficiency of C1q. More interestingly, the frequency of MBL deficiency was strongly decreased in the GBM group versus the control group (18% vs 32%). Suggesting that MBL deficiency is negatively correlated with GBM occurrence. To further evaluate the complement cascade we used an in-house gene expression dataset consisting of 276 glial tumor samples and 8 normal samples. Multiple gene expression analyses were performed on both a single-gene level and on a pathway level using different software tools to evaluate complement gene expression and patient survival. Results showed that glioblastoma with the worst prognosis showed a significant overexpression of the complement genes in tumor tissue on both a single gene and a pathway level. The results suggest that the complement system is involved in GBM disease. And that complement activation might lead to acceleration of tumor progression. Animal studies are needed to evaluate the role of the complement system in GBM.

P.148. GLIOBLASTOMA MULTIFORME IN A HIV PATIENT - A CASE REPORT

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INTRODUCTION: The management of glioblastoma multiforme (GBM) including concomitant radiochemotherapy in the immunocompromised HIV-positive patients is a therapeutic challenge, because of possible increased neurotoxicity, the potential additive lymphopenia under temozolomide and interactions of chemotherapy with highly active antiretroviral therapy. We report a 36-year-old man with human immunodeficiency virus (HIV), who was diagnosed for GBM. CASE REPORT: The patient, known to be HIV-positive for a few months, was admitted to hospital after an epileptic seizure, presenting with a left sided hemiparesis. Cranial magnetic resonance imaging revealed a right temporoparietal mass lesion. Tumour exstirpation was performed and the histopathological examination confirmed GBM. One week before initiation of the oncologic treatment we started antiretroviral therapy (raltegravir, emtricitabin and tenofovir). Subsequently concomitant radiochemotherapy according to the "Stupp-protocol" was performed, without developing serious hematological side-effects. Two months after the last adjuvant temozolomide course, tumour progression was detected and a second line chemotherapy with bevacizumab and irinotecan every two weeks was applied for six months. Then the general condition rapidly worsened, and the patient died 17 months after diagnosis of GBM due to tumour progression. CONCLUSIONS: Reviewing the literatur, there are only a few case reports concerning the managment of GBM in HIV-positive patients. With a survival of 17 months after diagnosis our patient had a favourable outcome, without any evident hematotoxicity or neurotoxicity which may be attributed to the concurrent HIV infection. This is an encouraging observation, indicating that concomitant radiochemotherapy is safe in HIV positive patients.

P.149. METRONOMIC CHEMOTHERAPY WITH TMZ ENHANCES THE INHIBITION OF ANGIOGENESIS ACCOMPANIED BY THE DOWN-REGULATION OF MGMT EXPRESSION IN ENDOTHELIAL CELLS

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Metronomic chemotherapy is a continuous low-dose administration of chemotherapeutic agents to minimize toxicity and target tumor-associated endothelial cells. This therapy is known to be beneficial to anti-angiogenic efficacy which is linked to the inhibition of tumor growth. In the present study, we compared the anti-angiogenicity of temozolomide in human umbilical vein endothelial cells (HUVECs) between conventional and metronomic treatment. Metronomic treat[[Unsupported Character - Codename]]ment of temozolomide (TMZ) (6.25 and 12.5 μM) showed increased inhibition of the proliferation of HUVECs compared to an equivalent conventional treatment of TMZ. The differential effects between conventional and metro[[Unsupported Character - Codename]]nomic treatment of TMZ were also noted in cell migration and angiogenic tube formation. Notably, the expression level of O6-methylguanine-DNAmethyltransferase (MGMT) was markedly reduced in the HUVECs treated with metronomic TMZ (12.5 and 25 μM) compared to cells treated with conven[[Unsupported Character - Codename]]tional treatment of TMZ. Accordingly, HUVECs treated with metronomic treatment of TMZ were more sensitive to TMZ treatment. Taken together, metronomic chemotherapy with TMZ enhances the inhibition of angiogenesis accompanied by the down-regulation of MGMT expression in endothelial cells.

P.150. HEMATOTOXICITY DURING CHEMORADIATION IN GLIOMA PATIENTS USING ANTI-EPILEPTIC DRUGS

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BACKGROUND: Epileptic seizures are a frequent symptom in patients. with a glioblastoma multiforme (GBM). Treatment with anti-epileptic drugs (AEDs) is troublesome for a number of reasons, not the least because of serious side-effects. Hematotoxicity, especially thrombocytopenia, is often reported for Valproic acid (VPA) and in lesser extent for Levetiractem (LEV). Thrombocytopenia also is a known side-effect of Temozolomide (TMZ) chemotherapy, which is the preferred chemotherapy for GBM patients. Severe thrombocytopenia results in postponing or even discontinue treatment with chemotherapy. Therefore, additional hematotoxicity of AEDs should be avoided. We hypothesize that patients using the combination of VPA and TMZ more often develop thrombocytopenia than patients using the combination of LEV and TMZ and patients not using any AED. METHODS: We included patients who were newly diagnosed with a. GBM and treated with standard combined treatment with radiation and TMZ. Patients used monotherapy VPA, monotherapy LEV or no AEDs. Clinical variables such as gender, age, dexamethason use and body-surface (m2) were documented. Thrombocyte count was measured each week during 6 weeks of standard combined treatment with radiation. and TMZ. Outcome measures were the absolute decrease in thrombocyte count during treatment and the frequency of reaching a clinical relevant thrombocyte count that resulted in postponing or ending treatment (<100). RESULTS: We included 182 patients; 59 used VPA (32%), 51 LEV (28%)

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and 72 no AEDs (40%). The patients that used LEV were significantly younger than the patients in the other two groups. Moreover, patients that used. LEV had a significantly larger body-surface (m2) than patients not using AEDs. These two confounders were controlled for in the analysis. Longitudinal analysis (using Generalized Estimated Equations) showed that the absolute thrombocyte count after treatment with TMZ was significantly lower in patients using VPA than in patients using LEV or no AEDs ($p = 0.014$ and $p = 0.005$, respectively). Clinical relevant thrombocytopenia (<100) occurred in 10 (17%) patients using VPA,. one (2%) patient using LEV and six (8%) patients not using AEDs. CONCLUSION: Patients using VPA report a larger decrease in thrombocyte count than patients using LEV and patients not using AEDs. These findings. appear clinically relevant.

P.152. GLIOMATOSIS CEREBRI (GC) TREATED WITH CHEMOTHERAPY: PRELIMINARY RESULTS OF A PHASE II STUDY EMPLOYING TEMOZOLOMIDE DOSE-DENSE

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BACKGROUND: The current WHO classification (2007) defines GC as a highly infiltrative glial lesion (usually astrocytic) that affects at least three lobes on MRI. GC is usually an aggressive neoplasm corresponding to grade III WHO. Due to the tumor extension, patients are usually not candidate to surgery. Radiotherapy can stabilize or improve neurologic functions, but a large volume of the brain is exposed to radiotherapy which may result in substantial toxicity. Chemotherapy with PCV or temozolomide standard schedule seems to be active as initial treatment. The aim of this study was to prospectively evaluate efficacy and toxicity of up-front dose-dense temozolomide in primary gliomatosis. PATIENTS AND METHODS: Inclusion criteria were as follows: clinical-radiological features of primary gliomatosis; biopsy-proven diagnosis; Karnofsky performance status score > 60. Temozolomide was administered in a dose-dense schedule (150 mg/m^2/day, one week on/one week off) until progressive disease. Neurological examination was performed monthly. Radiological response was evaluated on MRI every 3 months using modified McDonald criteria. RESULTS: 24 patients were enrolled: 17 males and 7 females, median age was 47 years (range: 21-72). Seizures were the most common presenting symptom: 16/24 (67%). Median KPS was 80 (range: 60-100). Among the 19/24 (79%) symptomatic patients, symptoms improved in 5/19 (26%), remained stable in 10/19 (53%) and worsened in 4/19 (21%). Radiological response was evaluable in 23/24 (96%) and was as follows: PR 4/23 (17%) and MR 6/23 (26%), for an overall response rate of 43%. SD was observed in 8/23 (35%) and PD in 5/23 (22%). PFSs at 6 and at 12-months were 61% and 22% respectively. Toxicity was mainly hematological, especially lymphopenia (grades 2 and 3). Radiotherapy as salvage therapy was performed in 11 patients. Response was evaluable in 7/11: MR 1/7 (14%), SD 4/7 (57%) and PD 2/7 (29%). Overall, median survival is 17 months with 11 patients still alive. 1p/19q codeletion, MGMT promoter methylation and IDH-1 mutation are ongoing. CONCLUSIONS: Chemotherapy with temozolomide is an option and this approach allows to delay radiotherapy in a subset of patients. Dose-dense temozolomide seems to compare favorably with the standard schedule.

P.153. MAJOR VAULT PROTEIN (MVP) MEDIATES STARVATION RESISTANCE OF HUMAN GLIOBLASTOMA CELLS VIA STABILISATION OF THE AKT/MTOR PATHWAY

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The 110 kDa major vault protein (MVP) represents the predominant part of a large ribonucleoparticle, the vault. Vaults are mainly located in the cytoplasm and almost ubiquitously expressed in eukaryotic organisms. MVP has been suggested to be involved in the regulation of multiple cellular processes including transport mechanisms, chemoresistance and intracellular signalling pathways. While in normal brain the expression is low, MVP levels are consistently upregulated in glioblastoma multiforme (GBM). Aim of this study was to investigate whether MVP/vaults have an impact on GBM cell growth and survival, including chemotherapy and stress responsiveness, and to clarify underlying molecular mechanisms. MVP was stably overexpressed in MVP-low H7 glioma cells. Ectopic and endogenous MVP expression was repressed by MVP mRNA-specific shRNA. Protein expressions were detected by immunofluorescence and Western blot. Consequences of MVP modulation on cell proliferation, survival, chemotherapy response and serum starvation with or without growth factor stimulation were analysed. Additionally, impact of MVP on subcutaneous and orthotopic tumour formation in SCID mice was tested. Ectopic MVP expression in H7 glioma cells did not substantially alter sensitivity against diverse chemotherapeutic drugs. However, endogenously and ectopically MVP-(over)expressing cells were impressively resistant to apoptotic cell death induced by serum-starvation, an effect reversible by shRNA-mediated MVP repression. Generally, PI3K downstream signalling, determined by AKT and S6 phosphorylation, was hyperactivated in MVP-positive as compared to control cells. Moreover, growth factor stimulation (EGF, serum) after starvation induced a stronger phosphorylation of AKT and S6 in MVP overexpressing cells. Accordingly, inhibition of mTOR via temsirolimus led to a complete blockade of S6 and 4EBP phosphorylation and reversal of MVP-mediated starvation resistance. In vivo experiments revealed that ectopic MVP expression enhanced subcutaneous tumour growth and reduced survival of SCID mice. Moreover, a distinct increase of AKT phosphorylation and a reduced apoptotic cell fraction was detected in orthotopic xenografts from MVP-overexpressing subclones. Our data elucidate a significant contribution of vaults/MVP to the malignant phenotype of human GBM cells by supporting enhanced survival under nutrient starvation mainly based on stabilisation of AKT/mTOR-mediated survival pathways.

P.154. CONCOMITANT RADIO CHEMOTHERAPY WITH CCNU IN NEWLY DIAGNOSED GLIOBLASTOMA: PRELIMINARY RESULTS OF A SINGLE INSTITUTION PHASE II STUDY

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BACKGROUND: When given concurrently with radiotherapy, Temozolomide has led to improved survival in GBM patients. This study was conducted to determine the relative contribution of concomitant CCNU in patients with newly-diagnosed GBM. PATIENTS AND METHODS: We identified all patients operated on for a supratentorial GBM and further treated with radiotherapy and CCNU based chemotherapy either in a concomitant (group 1) or adjuvant (group 2) setting. The primary endpoints of this study were progression-free survival (PFS), overall survival (OS) and the secondary endpoint was the toxicity. RESULTS: Fifty-one patients (group 1, $n = 25$; group 2, $n = 26$) were included in this study. The two arms were well balanced according to their baseline characteristics (including age, KPS, resection status). The median follow-up was 17.5 months (95% CI, 14 to inf months). A borderline statistically difference ($p = 0.08$) was observed according to the PFS between two groups (11 vs 7 months). The median survival OS was 18 months (95% CI 13.6 and 24.7 months) with RT plus CCNU and 11 months (95% CI 10.9 and 16.1 months) with adjuvant group, $P = 0.09$ by the log-rank test. Hematological toxicity was absent during concomitant chemo-radiation and mild (6%) in adjuvant therapy. CONCLUSIONS: Concurrent and adjuvant CCNU is associated with improved survival compared to adjuvant CCNU alone. These results highlight the potentiation of radiation effect by CCNU in the clinical setting.

P.155. GLIOBLASTOMAS AFTER BEVACIZUMAB: HISTOLOGICAL AND MOLECULAR CHARACTERISTICS

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Bevacizumab has been approved for the treatment of recurrent glioblastoma in various countries. The phase III registration trial assessing the addition of Bevacizumab to standard chemoradiotherapy in newly diagnosed glioblastomas has completed recruitment. Salvage treatment of glioblastoma patients after Bevacizumab failure, however, remains a challenge. We aimed at characterizing histological and molecular characteristics associated with Bevacizumab failure in glioblastomas. We. collected paired tissue samples from primary and recurrent tumors obtained from 12 patients with glioblastoma ($n = 11$) or anaplastic astrocytoma ($n = 1$) before and after Bevacizumab treatment, and 14 non-Bevacizumab-treated patients as a reference group. All tissue samples were analyzed for histological features and molecular markers. In addition, clinical records and magnetic resonance images were reviewed. Histologically, recurrent tumors after Bevacizumab showed more commonly a decreased blood vessel density and reduced glomeroloid microvascular proliferations when compared to recurrent tumors after standard radio- and temozolomide chemotherapy. Molecular genetic

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studies of the respective tissue specimens are currently under way. Histological and molecular analyses of paired tumor tissue samples from glioma patients before and after Bevacizumab treatment, combined with clinical and radiological correlates, may provide hints for therapy escape mechanisms that can then be validated in preclinical models and may serve as a basis for the design of therapeutic approaches in recurrent malignant gliomas after bevacizumab.

P.156. IS PSEUDOPROGRESSION (PSP) IMPACTED BY A VERY EARLY PROGRESSION (VEP)? A RETROSPECTIVE COHORT STUDY

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BACKGROUND: After the concomitant chemoradiotherapy, the evaluation of the tumor control in glioblastoma (GBM) is impacted by the pseudoprogression (psP). The psP is a widely accepted concept with an uncertain incidence (7 to 31%) and involves the use of subsequent imagery. Taking into account tumor assessment from surgery to progression, this study aims to refine the definition of the psP in a homogenous group of GBM. Moreover we attempt to discern how the tumor evolution before radiotherapy (RT) could help to identify the psP. METHODS: A retrospective cohort of patients with newly diagnosed GBM, treated from 2008 to 2010 by RT and concomitant temozolomide (TMZ) followed by adjuvant TMZ was studied. MRI were evaluated at multiple times: preoperative, postoperative, prior to RT when available, 1 month after RT and every 2 month until progression. Early progression (EP) was defined by a progression on the RT + 1 MRI. Pseudoprogression (psP) was defined as an EP that is followed either by a stable status on the RT + 3 and RT + 5, either by a response status on the RT + 3 or the RT + 5. True early progression (TEP) was defined by an EP that is followed by a progression status on the RT + 3 or RT + 5 when assessable. Very early progression (VEP) was defined by a progression during the interval between surgery and RT. RANO criteria were applied. Progression free (PFS) and overall survival (OS) were measured by Kaplan-Meier curves and Log-rank test was used to detect significant differences. RESULTS: Analysis of the first 75 patients was achieved. Based on postoperative MRI, macroscopically total resection, partial resection and biopsy were realized for respectively 19 (25.3%), 49 (65.3%) and 7 (10.3%) patients. There was no available MRI between surgery and RT in 17 cases. On the 58 analyzable patients, 29 were in EP (50%) including 10 psP (17.2%) and 19 TEP (32.7%). The PFS in the TEP group was significantly lower compared to the no EP ($p < 0.001$) and the psP ($p = 0.002$) group. No statistically different was found for the OS. Between no EP and psP groups, no distinct outcome was found for PFS and OS. In 12 patients, two MRI were available between surgery and RT. VEP was observed in 10/12 cases. 1 VEP was lost to follow-up. On the 9 analyzable patients, subsequent imagery revealed 2 psP, 2 TEP and 5 no EP. Taking into account the VEP, 2 patients were not in progression on the RT + 1 MRI and changed their status from psP to no EP. CONCLUSION: The incidence of the psP tends to be lower in this cohort than in previous studies. PFS doesn't significantly differ by comparing the no EP and psP group. Taking into account the pre-RT period, a subset of psP status could rather be considered as no EP, decreasing the incidence of psP. This preliminary analysis support the role of the tumor assessment between surgery and RT. Full analysis of the cohort will be presented.

P.157. SELECTION OF SUITABLE REFERENCE GENES FOR EXPRESSION STUDIES IN PRIMARY, SECONDARY AND RECURRENT HUMAN GLIOMAS USING QUANTITATIVE RT-PCR

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BACKGROUND: Quantitative RT-PCR (RT-qPCR) is frequently used to analyse gene expression. In human astrocytomas, three studies have been performed validating reference genes, however, no systematic analysis of suitable endogenous control genes exists for recurrent tumors and under treatment conditions. Therefore, this analysis enables longitudinally designed studies (e.g.,astrocytomas before and after malignant transformation). METHODS: This study aimed to test the best six reference genes out of the other studies (RPL13A, GAPDH, SDHA, POLR2A, ACTB, and TBP) for their expression stability in the following groups: (i) diffuse astrocytoma WHO Grade II, anaplastic astrocytoma WHO Grade III, and glioblastoma (GBM) WHO Grade IV; (ii) primary GBM, and secondary GBM; (iii) primary glioma, and recurrent glioma; (iv) with chemotherapy (CTx), and without CTx. Tissue samples (n = 10 per group) were obtained from our tumor tissue bank. After RNA extraction and transcription into cDNA, all qPCRs were done twice in duplicate. The statistical softwares geNorm and NormFinder were used to select the most stable candidate genes, whereby both the intra- and intergroup variation of candidate genes were modeled. RESULTS: The C_T-values of the reference genes analyzed show different transcription levels in all groups, ranging from 14 - 16 (ACTB, GAPDH, RPL13A, low expression) to 20 - 23 (SDHA, POLR2A, TBP, high expression). Our results indicate that SDHA displays the most stable values for recurrent astrocytomas with rising tumor grade (WHO° ll to III to IV). Furthermore, most other genes are differentially regulated in primary GBM compared to secondary GBM. ACTB shows the most stable results as a gene which is low expressed in brain tumor tissue. CONCLUSION: Taken together, our data show the relevance of previous validation of candidate control genes for each experimental design and indicates that the most suitable housekeeping genes are SDHA and ACTB for quantitative PCR analysis in glioma tissue.

P.158. COMPLETE, BUT NOT PARTIAL RESECTION IS IMPORTANT IN THE ERA OF RADIOTHERAPY, CONCOMITANT AND ADJUVANT TEMOZOLOMIDE FOR GLIOBLASTOMA PATIENTS

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PURPOSE: Tumor resection followed by concomitant and adjuvant radiochemotherapy with temozolomide (RT/TMZ◇TMZ) is considered standard of care for glioblastoma. Still, patterns of care are highly variable. Moreover, the benefit of partial resection compared to biopsy only is still unclear. This multicenter observational study was conducted to assess currently applied treatment strategies and to identify prognostic factors with a special focus on the influence of extent of resection and *MGMT* promoter methylation. EXPERIMENTAL DESIGN: Patients with newly diagnosed glioblastoma were enrolled between 2006 - 2010. Histology was centrally reviewed, *MGMT* promoter methylation status was assessed by methylation-specific PCR. Data were collected and analysed with the help of a central data management unit. Survival analyses were performed with the Kaplan-Meier method. Endpoints were overall survival (OS) and progression free survival (PFS). Prognostic factors were assessed with proportional hazards models. RESULTS: In a total of 369 patients, 40.1% received a total resection, 40.1% a partial resection and 19.8% underwent biopsy only. Surgery-related morbidity was lower after biopsy (1.4% vs. 11.5%, $p = 0.006$). 65% of patients received RT/TMZ◇TMZ, 19.2% RT alone, 4.1% TMZ alone and 11.7% supportive care only. Patients $\leq$60years and KPS $\geq$ 90 were more likely to receive open tumor resection and RT/TMZ◇TMZ ($p < 0.01$). Median PFS and OS of all patients were 6.8 months (95%-CI 6.2-7.3) and 12.7 months (95%-CI 11.3-14.2). Median OS (PFS) of subgroups was as high as 27.7 months (14.8 months) for patients with *MGMT* methylated tumors after complete resection plus RT/TMZ◇TMZ to as low as 3.0 months (2.4 months) for biopsied patients receiving supportive treatment only. Favorable prognostic factors for OS were *MGMT* promoter methylation (RR = 0.43; $p < 0.001$), RT/TMZ◇TMZ treatment vs. no treatment (RR = 0.17, $p < 0.001$), age $\leq$60 years (RR = 0.48; $p < 0.001$), a KPS $\geq$ 70 (RR = 0.46; $p < 0.001$) and complete resection vs. biopsy (RR = 0.59; $p = 0.002$). Incomplete resection was as good as biopsy only, both in the whole study population and in a large subgroup of 240 patients receiving RT/TMZ◇TMZ. *MGMT* methylation and complete resection continued to be of independent prognostic importance. CONCLUSION: Our study confirms superior OS in case of *MGMT* promoter methylation, RT/TMZ◇TMZ treatment and complete tumor resection. Incomplete resection does not significantly improve OS as compared to biopsy only.

P.159. TREATMENT AND SURVIVAL OF ANAPLASTIC GLIOMA

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INTRODUCTION: Anaplastic gliomas are representing around one tenth of all malignant gliomas. They are treated with surgery and radiotherapy. In last years, systemic therapy is increasingly used in treatment of those tumours.

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We are reporting results from G III glioma treatment in Slovenia from 2000 to 2008. PATIENTS AND METHODS: We obtained data from the Cancer registry of Slovenia and our treatment charts, including all anaplastic astrocytomas (AA), oligodendrogliomas (AO) and oligoastrocytomas treated at Institute of Oncology Ljubljana. RESULTS: In this time 123 patients were treated. There are 74 AA s, 45 AO s and 4 oligoastrocytomas, with median age of 44 years (SD 16 years), 4 patients were lost to follow up. The least patients (6) were treated in 2006, and the most (19) in 2007, averaging 14 patients per year. All patients had prior surgery, 21 biopsies, 54 subtotal resections and 48 gross total resections. After surgery, most patients were in performance status of 0 and 1 (79) and 13 in performance status of 3 and 4. Of 123 referred patients 107 received radiotherapy, 76 received chemotherapy. Of patients received chemotherapy 3 did not received radiotherapy. In patients with AA the most common chemotherapy was temozolomide 37/41 patients, while 31/34 patients receiving chemotherapy for AO received PCV. In both groups, younger patients fared better, as well as those receiving radiotherapy and chemotherapy. Performance status was associated with better survival as well as extent of surgery in whole group and in AA group, but not in AO group. Median survival in AO group was 10 years (SD 25 months) and in AA group 5 years (SD 12 months). In patients with AO there was no difference in survival whether chemotherapy was included or not, but median survival vas significantly higher in AA patients receiving chemotherapy (one year for patients not receiving chemotherapy while median survival was not reached in patients receiving temozolomide. Most of patients with recurring tumours, received either surgical or systemic treatment for recurrences. Two patients even had a pathologically confirmed recurrence of AA outside CNS (bones). DISCUSSION: We can say that our results in treatment of anaplastic gliomas especially AO are encouraging, but we must concede the fact, that patients with very poor performance status were not seen at our institution, but were referred for supportive care straight from the multidisciplinary team. Due to same reason we failed to show impact of radiotherapy on survival. Inclusion of temozolomide in 2005 in treatment of AA has improved survival of those patients, though other chemotherapies (PCV and BCNU were used) might also have an impact. Survival is probably higher also because of the use of salvage treatment.

P.160. METABOLIC ANALYSIS OF GLIOBLASTOMA XENOGRAFTS AFTER ANTI-ANGIOGENIC TREATMENT

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Glioblastoma multiforme (GBM) is characterized by extensive neovascularization and endothelial cell proliferation. Treatment of GBM with bevacizumab, a monoclonal antibody against vascular endothelial growth factor, showed promising therapeutic results in initial clinical trials. However tumor recurrence is inevitable suggesting major adaptation mechanisms that allow tumor cells to escape anti-angiogenic therapy. We have previously shown in experimental patient derived GBM xenografts that bevacizumab reduces blood flow, increases hypoxia and lactate levels as well as tumor cell invasion into the brain parenchyma. These data suggest that anti-angiogenic treatment induces a metabolic switch in GBMs leading to a more glycolytic energy metabolism. The consequences in terms of tumor growth and the connection with increased invasiveness are poorly understood. Here we used $^{13}C_6$ glucose injections into tumor-bearing rats followed by liquid chromatography-mass spectrometry (LC-MS) based metabolomics analysis to determine metabolic flux and steady state of glucose derived metabolites in tumor extracts after anti-angiogenic treatment. The results and conclusions of these analyses will be presented.

P.161. CONCURRENT CHEMORADIOTHERAPY IN PATIENTS WITH GLIOBLASTOMA MULTIFORME- A SINGLE INSTITUTION EXPERIENCE

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INTRODUCTION: Despite aggressive multimodal treatment median survival of patients with glioblastoma multiforme (GBM) is approximately 12 months. Adjuvant treatment with temozolomide (TMZ) given concurrently with radiotherapy followed by 6 cycles of TMZ monochemotherapy prolongs survival for 2.5 months and it is currently used as standard treatment for newly diagnosed GBM. The single institution experience with adjuvant concurrent chemoradiotherapy in GBM patients is presented below. PATIENTS AND METHODS: From September 2006 till September 2010 58 patients (29 male and 29 female) with newly diagnosed GBM were treated in our hospital. The treatment protocol consisted of radiotherapy (6000 cGy in 30 fractions with ^{60}Co) and concurrent chemotherapy with TMZ 75 mg/m^2/day. Four to six weeks after concurrent phase MRI evaluation was done, and patients with regression or stable disease continued TMZ monotherapy 150-200 mg/m^2/day/5 days for 6 cycles given in 28-day intervals. Treatment toxicity was evaluated according to the Common Terminology Criteria for Adverse Events, version 4.03. Survival was calculated using Kaplan Meier method, and relevant stratifying variables were entered into Cox-proportional-hazards models to predict survival. We considered p values less than 0.05 as statistically significant. RESULTS: Median age of our patients was 58 years (range 34-75). Fifty four patients (93 %) had undergone maximal surgical reduction. Median radiotherapy dose was 6000 cGy and 44 patients (76%) received radiotherapy without interruption. Thirty nine patients (67%) received full course of concurrent TMZ; 19 patients (33%) experienced toxicity which caused chemotherapy interruption or discontinuation. After conrurrent phase and MR evaluation, 25 patients (43%) continued with TMZ monotherapy, 10 patients (17%) received salvage, nitrosourea- based chemotherapy due to disease progression and 23 patients (40%) continued with best supportive care due to clinical deterioration. Treatment toxicity occured mainly during the concurrent phase (Grade 1-4 thrombocytopenia in 26% patients and Grade 1-4 neutropenia in 7% patients), and caused discontinuation of therapy in 9 patients (15%). At a median follow-up of 56 months, median survival was 9.1 months. Two-year survival rate was 13.8 %. Survival longer than four years was recorded in 3 patients (5.1 %). On multivariable Cox regression analysis, the independent clinical prognostic factors of survival included postoperative ECOG performance status ($p < 0.0001$) and female gender ($p = 0.045$). CONCLUSION: Our results with concurrent chemoradiotherapy in newly diagnosed patients with GBM do not correlate with published data and show inferior two- year and overall survival. Larger patient series are needed to clearly identify the efectiveness of concurrent chemoradiotherapy and clinical prognostic factors of survival.

P.162. A PHASE II TRIAL EVALUATING THE EFFECTS OF BORTEZOMIB IN PATIENTS WITH RECURRENT MALIGNANT GLIOMAS TREATED PRIOR TO SURGERY AND THEN BORTEZOMIB AND TEMOZOLOMIDE POST-OPERATIVELY

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BACKGROUND: NF-Kappa B is one of the mechanisms of resistance for Malignant Gliomas. A few trials have assessed Bortezomib in the. treatment of malignant gliomas with limited activity. This may in part be due to limitations in dose escalation from peripheral neuropathy. We performed a phase II trial with the goal of measuring Bortezomib in tumor tissue and also its effects on NF-Kappa B. METHODS: Patients felt to be surgical candidates were enrolled after signing an IRB approved consent. They were treated with Bortezomib 1.7 mg/m^2 IV on day 1, 4 and 8 and then had surgery on day 8 or 9. Approximately, 14 days post operatively, patients were started on temozolomide 75 mg/m^2 PO on days 1-7 and 14-21; on day 7 and day 21 they received Bortezomib 1.7 mg/m^2 (1 cycle was 1 month). Treatment continued until progression. If $\leq$1 patient had a PFS at 6 months the trial would be stopped. RESULTS: 10 patients were enrolled (8 M and 2 F). Median age and KPS were 50 (42-64) and 90% (70-90). All but 1 patient went to surgery, one had an intracranial hemorrhage. The median number of cycles post operatively was 2 (1-4), with two patients discontinuing for wound infection (post 3 cycles, not restarted due to prolonged delays) and meningitis (post 2 cycles then withdrew from trial). Six patients are deceased. Trial was stopped as no patient had a PFS-6. PK analysis revealed measurable drug levels in tumor tissue. CONCLUSION: Post operative treatment with temozolomide and Bortezomib did not have any activity. Bortezomib can achieve measurable drug levels in tumor but may not be sufficient for anti-tumor activity. Tissue will be assessed for Bortezomib effects on NF-Kappa B.

P.163. TREATMENT STRATEGIES OF GLIOMAS WHO GR. III. FOUR YEARS EXPERIENCES OF ONE ONCO-CENTRE.

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INTRODUCTION: Anaplastic gliomas WHO grade III comprise 6 – 10% of all newly diagnosed adult primary brain tumours. They are sorted

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into three types: anaplastic astrocytoma (AA), anaplastic oligoastrocytoma (AOA) and anaplastic oligodendroglioma (AO). Although current WHO classification gives seemingly clear definition for the diagnosis of both grade and type, but diagnosis procedure are not under little subjectivity influence (differentiation of grade II and III astrocytoma, classification of oligodendroglial tumours with necrosis, diagnosis of a mixed glioma). Moreover last WHO classification excluded a necessity of necrosis in histologic features for setting of glioma WHO gr. IV diagnosis. Studies of gliomas gr. III have not made unequivocal accepted advices for oncologic treatment. According molecular genetic, cytogenetic, imunohistochemical investigations, as IDH, 1p/19q, MGMT, gliomas WHO gr. III are sorted on tumours. METHOD: From 2007 March 31 to 2011 March 31 we selected prospectively patients with gliomas gr. III. Information about surgeries, patient clinical condition, MRI, PET/CT FLT, and results of histological, imunohistochemical, molecular genetic and cytogenetical investigations were gathered. The first aim was radical surgery. Biopsy was recommended for above 75-year old patients, patients with KS $<$ 60, or unresecable tumours. Patients with AA in good condition (PS $>$ 70) after radical resection were recommended concomitant chemo-radiotherapy, ensued adjuvant chemotherapy. Rest of patients was recommended radiotherapy and followed adjuvant chemotherapy. Rational was based on presence of oligodendroglial tumour component, MRI imaging and clinical conditions. The clinical and MRI follow-up of patients after first surgery was be carried out. RESULTS: We collected heterogenic group of up to 50 patients. About 70% patients underwent surgery and 30% biopsy. Patients with AA, which underwent radical surgery and concomitant chemo-radiotherapy had favourable prognosis match with patients after biopsy and concomitant chemo-radiotherapy. By secondary gliomas gr. III, surgery targeted tumor "hot spots" revealed by MRI and PET/CT FLT imaging. Repeated or new administered chemotherapy of recurrent tumour had good prognosis. It was also confirmed a favourable impact of surgical radicality oligodendroglial tumour component, loss of 1p/19, methylation of MGMT promoter, mutation of IDH. CONCLUSION: For a new histologic features of glioma WHO gr. IV, percentage of revealed gliomas gr. III decreased. Authors have on mind a limited number of followed patients, but we want to present our experience with this very intricate problem. We endeavor to adjust our treatment strategy for every mentioned subgroup Support in part by grant of IGA of Ministry of Health, Czech Republic No. NT11065-5/5/2010.

P.164. BEVACIZUMAB AND IRINOTECAN IN THE TREATMENT OF PATIENTS WITH RECURRENT GLIOBLASTOMA

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BACKGROUND: The patients with recurrent glioblastoma have poor prognoses. The median survival of patients in this group in historic data did not exceed 3-6 months. Bevacizumab, a monoclonal antibody targeting the vascular endothelial growth factor (VEGF), has shown significant activity in a subset of patients with high grade gliomas (HGG). Irinotecan has demonstrated some activity against recurrent glioblastoma, with response rates of 0%-15% and 6-month PFS of less than 20%. The main goal of this trial is to assess the efficacy of combined chemotherapy of bevacizumab & irinotecan in patients with recurrent glioblastoma. METHODS: 12 patients with glioblastoma, relapsing after radiotherapy and temozolomide were included in this study. These pts were treated with bevacizumab - 5 mg/kg intravenous on day 1, every 2 weeks + irinotecan - 125/mg/m^2 intravenous on day 1, every 2 weeks. Before first treatment and every 6-week patients were evaluated with a physical examination and magnetic resonance imaging. Radiological responses were assessed based on RANO criteria. The main aims of this study were objective response (OR) - complete response (CR) + partial response (PR), progressive-free survival (PFS), median of survival (mOS), 6-month and 1-year survival. RESULTS: 5 patients (41,7%) achieved partial response, 5 (41,7%) showed disease stabilization in the brain and 2 (16,6%) showed progression. Progressive-free survival was 5,5 months. Median overall survival was 9 months. 6-month survival was - 66,6%, 1 year survival was 25%. Significant adverse events were infrequent and included one patient who developed thrombotic thrombocytopenic purpura. CONCLUSIONS: Previous results of our study showed promising high efficacy of bevacizumab & irinotecan in patients with recurrent glioblastoma, with reasonable tolerability. Further investigation is to be expected.

P.165. BONE MARROW METASTASIS AND EPIDURAL SPREAD FROM CEREBRAL ANAPLASTIC OLIGODENDROGLIOMA

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BACKGROUND: Few cases of anaplastic oligodendroglioma with systemic metastasis are reported in the literature. Most often in metastasising cases, spread to regional cervical lymph nodes is described. Distant metastasis to inner organs and bone marrow involvement is exceedingly rare and carries a very poor prognosis. METHODS: We report a case of frontal cerebral oligodendroglioma with relapse and malignant transformation to anaplastic oligodendroglioma more than 10 years after initial diagnosis and spread to bone and bone marrow. RESULTS: The patient, a then 27 years old male, was initially diagnosed with a grade II oligodendroglioma in 1999 and underwent surgery. Relapse in 2001, treated with surgery and adjuvant radiation therapy. The patient presented in March 2011, hence 12 years after, with a cerebral relapse, which was partially removed by renewed surgery. Histopathological diagnosis showed grade III anaplastic oligodendroglioma. In July 2011, the patient noticed lymphadenopathy on one side of the neck. Biopsy showed metastasis from anaplastic oligodendroglioma, positive for S-100 and synaptofysin. Simultaneously, the patient presented severe thrombocytopenia, and bone marrow biopsy showed suppression and infiltration by anaplastic oligodendroglioma. PET-CT scan showed cervical lymph node metastasis and bone metastasis in Th9 and right hip. Despite thrombocytopenia, temozolomide therapy was initiated. Response both intracranially and systemically was obtained during 5 cycles of temozolomide, with normalization of thrombocyte count. Subsequently the patient developed progressive back pain and renewed PET-CT scan showed massive tumour involvement of the entire spine and spinal MRI showed partial collapse of Th9 and epidural spread. The patient received 3 Gy x 10 at level Th9-10, but cessation of further chemotherapy ensued due to deterioration of the general condition of the patient and relapse of thrombocytopenia. DISCUSSION: Systemic spread with involvement of bone and bone marrow from an anaplastic oligodendroglioma is extremely rare, and development of epidural compression from tumour involved vertebrae and bone marrow rather than from CNS spread has not before been reported in the literature.

P.166. DETECTION OF HUMAN CYTOMEGALOVIRUS (HCMV) IN TUMOR AND BLOOD SAMPLES OF GLIOBLASTOMA PATIENTS UNDERGOING ANTIVIRAL THERAPY WITH VALGANCICLOVIR;-IMPROVED SURVIVAL IN PATIENTS WITH LOW HCMV IGG ACTIVITY

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Glioblastoma is the most common malignant brain tumor in adults and is nearly always fatal. Emerging evidence imply that human cytomegalovirus (HCMV) nucleic acids and proteins are present in 90-100% of glioblastoma, medulloblastoma, colon, breast and prostate cancer, which may offer new therapeutic strategies. We recently reported that antiviral therapy against HCMV of medulloblastoma tumors, significantly prevented tumor growth in vitro and in vivo. In an explorative clinical phase I/II trial we examined the safety and potential efficacy of valganciclovir treatment against HCMV in glioblastoma patients diagnosed with HCMV in their tumors (VIGAS). We observed trends but no significant effects of antiviral therapy on tumor growth at 12 and 24 weeks, but an unexpectedly high overall survival in long-term treated patients at 2 and 4 years follow up. We collected blood cell samples from the VIGAS patients for analyses of HCMV DNA, RNA, IgG and IgM at base line and at 3, 12 and 24 weeks during treatment with placebo or valganciclovir. Here, we report that all patients were HCMV protein positive in the tumor and had at least one HCMV positive DNA blood sample. However, 28.6% of these patients were IgG negative for HCMV. The median overall survival was significantly higher among CMV IgG negative patients compared to HCMV positive patients independent of treatment ($p = 0.0273$), 26% were IgM positive and 66% were HCMV RNA positive in blood samples; no association was observed to survival. Among healthy controls, 74% were IgG positive, none was IgM positive. Valganciclovir treatment did neither affect DNA or RNA levels for HCMV in blood or IgG titers, but all IgM positive patients who were treated with valganciclovir became IgM negative. Our results indicate that the activity of HCMV is higher in glioblastoma patients than in healthy

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blood donors, and that low HCMV IgG activity is associated with improved outcome, and these patients demonstrate significantly improved survival.

P.167. PROGNOSTIC FACTORS IN GLIOBLASTOMA

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BACKGROUND: Glioblastoma (GBM) is the most common malignant primary brain tumor. However there is limited data on specific prognostic factors in these patients. METHODS: After obtaining IRB approval, the Cleveland Clinic Brain Tumor and Neuro-Oncology Center's database was used to identify patients with histologically confirmed GBM who were 18 years at the time of diagnosis. Multivariable analysis was conducted to identify independent predictors of survival using a Cox proportional hazards model and a stepwise selection algorithm with $p = .05$ as criteria for entry and retention. RESULTS: 929 patients diagnosed with glioblastoma (1991-2011) were included for analysis. Overall 59% of patients were male and median age at diagnosis was 66 (range 18-96). 37% of patients had biopsy only whereas 29% had gross total resection of their disease, 8% had near total resection, and 21% had subtotal resection; the degree of resection was unspecified for 5% of patients. 77% of patients received radiation. Excluding patients who died within one month of diagnosis, 28% of patients received concurrent or adjuvant chemotherapy and 30% received both (chemotherapy was primarily temozolomide-based); overall, 20% of patients had no post-operative treatment, 22% received RT only, and 58% received RT + concurrent and/or adjuvant chemotherapy. 89% of patients are reported to have died. Median overall survival is estimated to be 9.3 months (95% C.I. 8.5-10.0) with and 24-month survival estimated to be 41% + 2% and 14% ±1%.> CONCLUSIONS: On multivariate analysis, biopsy, increasing age, poor performance status, multifocal tumors, more than one lobe involvement, hypertension, coronary artery disease and lack of seizure at presentation were poor prognostic features (excluding chemotherapy and radiation).

P.168. ANTIANGIOGENIC TREATMENT (AT) IN GLIOBLASTOMA MULTIFORM TUMORS (GBM): IMAGING BUT ALSO CLINICAL ASSESSMENT: CORRELATION BETWEEN MCDONALD, RANO AND RECIST 1.1 CRITERIA

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INTRODUCTION: Since the publication in 2007 of the AT results in recurring high grade glioma, this treatment has been widely used and enables some improved survival benefit. The MRI evaluation is a standard practice to follow the treated patients. In 10-20%, we observed discrepancies between T1Gado enhanced (T1G), T2 sequences and the neurological patient outcome. Other tools as RANO including T2/Flair parameters or RECIST 1.1 criteria have to be compared each other and to the reference tool. OBJECTIVE: to compare T1G alone, McDonald's, RANO and RECIST 1.1 criteria every 3 months and clinical outcome in recurrent GBM. PATIENTS AND METHODS: GBM previously treated by radiotherapy (RT) and continuous temozolomide (TMZ) then monthly TMZ were included into the study. When recurrence occured, Avastin 10 mg/kg and Irinotecan 125 mg/m^2 were administered every 2 weeks until progression. MRI, clinical examination and steroïd changes were performed every 3 months. Results n= 45; Performans Status was 0-1 in 53%, 2 in 38% and 3 in 9%, median age 55 (35-78), all the pts had GBM tumors. Total macroscopic resection, incomplete resection and biopsie alone were performed in 56, 16, 24%, resp. Initial treatment was RT-TMZ and monthly TMZ in 93%, RT and CT in 7%. Progression under Stupp protocol occurred after 3, 6, 9 and > 12 mths in 44, 24, 4 and 18% of the pts, resp. 57% of the population received steroid at the inclusion. The median number of cycles of AT was 6 (2-29). According to McDonald's criteria, the efficacy was 17%, 44% and 39% for PR, SD and PD, resp.; according to RANO criteria, 9%, 40% and 51% of the pts were in PR, SD or PD, resp.; according to RECIST 1.1 criteria, we observed PR, SD and PD in 16, 67 and 16% of the cases, resp. The concordance assessed by Kappa coeff. was 0.76 between McDonald's and RANO criteria, but only 0.41 between McDonald's and RECIST criteria. The median progression time was 3.9 mths. The median survival was 18.3 mths from diagnosis and 5.6 mths from the onset of the treatment. DISCUSSION-CONCLUSION: This study gives us the opportunity to confirm that MRI T1G sequence is not enough to assess antiangiogenic drugs efficacy. Although McDonald's criteria remain the tool generally used, antiangiogenic drugs lead to extend MRI evaluation to T2 or FLAIR sequences according to RANO criteria. The concordance favours this latest scale. In our experience, RECIST 1.1 criteria match worse with Mc Donald's or RANO's criteria. We have to check if adjunction of T2/Flair sequence to classical RECIST 1.1 version could improve the sensibility of the method.

P.169. HDAC INHIBITOR SCRIPTAID AND PROTEASOME INHIBITOR G5 SYNERGISTICALLY ENHANCE CELL DEATH IN MALIGNANT GLIOMA CELL LINES

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The dismal prognosis of patients bearing high-grade gliomas warrants development of alternative treatment strategies. Small molecule inhibitors targeting specific pathways have shown potential in treatment of various forms of cancer, however, for glioblastoma the results from clinical trials have been disappointing. Studies suggest that combination therapies are required to achieve therapeutic benefit and that molecular characteristics of the tumor should dictate the choice of treatment. The HDAC inhibitor Scriptaid has been shown to inhibit glioma cell proliferation and promote cell death in a JNK-dependent. manner as well as to decrease telomerase activity. Therefore, this compound might be of interest for adjuvant treatment in patients with high-grade glioma. In the present study the HDAC-inhibitor Scriptaid was examined alone and in combination with other targeted drugs as well as Temozolomide (TMZ) and radiotherapy (RT). The following targeted drugs were selected for this study: G5 and bortezomib (both proteasome inhibitors), apoptosis-inducing effector molecule TRAIL, DNMT inhibitor Decitabine, 2-deoxy-Dglucose (2-DG) (glyclolysis-inhibitor). Therapeutic efficacy of the combination treatments was. assessed on a panel of 16 patient-derived glioma cell cultures in different. combinations and concentrations. In this drug-screening assay, cells are. cultured in defined serum-free medium which was shown to be essential for retaining the copy number variations profile of the original tumor for multiple passages. Sensitivity to Scriptaid when used as a single agent was seen in 75% of the tested cell cultures. In the combination studies with Scriptaid synergistic cell killing was observed with 2-DG, TRAIL, Bortezomib and Decitabine. Highest. synergy was seen with the combination of Scriptaid and G5, in this case in 88% of cell lines synergistic cell kill was observed. Interestingly, less synergy was seen when Scriptaid was combined with Temozolomide or Radiotherapy. CONCLUSION: This study shows Scriptaid is a potent HDAC Inhibitor. The combination of Scriptaid and G5 showed great synergy in treating primary cultures of glioblastoma tumors. Further studies on this treatment combination are aimed at molecular determinants to identify responders to this targeted treatment.

P.170. TRAIL IN COMBINATION WITH PROTEASOME INHIBITION SHOWS SYNERGISTIC CYTOTOXICITY IN GLIOBLASTOMA SUBSETS DEFINED BY RNA EXPRESSION PROFILING

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The dismal prognosis of patients bearing high-grade gliomas warrants development of alternative treatment strategies. Small molecule inhibitors targeting specific pathways have shown potential in treatment of various forms of cancer, however, for glioblastoma the results from clinical trials have been disappointing. Studies suggest that combination therapies are required to achieve therapeutic benefit and that molecular characteristics of the tumor should dictate the choice of treatment. In the present study the apoptosis-inducing effector molecule TRAIL was tested alone and in combination with conventional treatment and different types of targeted drugs such as HDAC inhibitors and proteasome inhibitors. Therapeutic efficacy of these combinations was assessed on a panel of twenty patient-derived glioma cell cultures in different combinations and concentrations. In this drug-screening assay, cells are cultured in defined serum-free medium which was shown to be essential for retaining the copy number variations profile of the original tumor for multiple passages. Treatment with TRAIL alone conferred variable responses but non-responders were seen in 12 of the 20 cell lines tested. FACs analysis for the TRAIL receptor DR5 revealed a positive correlation between DR5 expression and TRAIL sensitivity. Furthemore, lack of apoptosis-inhibiting protein Bcl-2 expression correlated with response to TRAIL in most but not all cases. In the combination studies with TRAIL, synergistic cell killing was observed using Daidzein (an Isoflavone) and the proteasome inhibitors Bortezomib and G5.

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Combination with the standard treatment modalities radiotherapy and TMZ showed additive or synergistic effects in only few cases, and even antagonistic effects in some cases. Supervised cluster analysis was performed on a small set of genes published by Bredel et al (2009) that showed correlation to clinical outcome. This was seen most clearly in G5 monotherapy and in TRAIL combined with Temozolomide. CONCLUSION: Targeting apoptosis via TRAIL is a promising treatment in Oncology in which overcoming resistance to TRAIL is key. This study shows that TRAIL and G5 form a potent synergistic combination in treating glioblastoma cell lines. Gene-expression profyling, Bcl-2, as wel as DR5 expression can be applied as molecular determinants to identify responders.

P.171. A NOVEL METRIC OF PATIENT-SPECIFIC RESPONSE TO TREATMENT FOR GLIOBLASTOMA DISCRIMINATES PATIENTS WITH PSEUDO-PROGRESSION

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Purpose/Objective(s): A complete resolution of enhancing tumor on T1 weighted contrast MRI of patients with glioblastoma following resection and chemoradiation has been demonstrated to predict for longer survival. We have developed a novel method for discriminating time to progression following therapy for glioblastoma using computational models of the proliferative and diffusive tumor burden that account for the unique geometry and biology of each patient's tumor. Using kinetic models informed by patient specific measurements, we simulate the growth of an untreated tumor and estimate the number of "Days Gained" by the therapy. The goal of this study was to determine whether this metric of patient response would assist in evaluating patients who have residual T1 enhancing lesions following treatment with concurrent chemoradiation for glioblastoma. MATERIALS/METHODS: 28 patients with glioblastoma were prospectively enrolled prior to chemoradiation in our IRB approved image database study from 2003 to 2009. All patients underwent chemoradiation therapy at the University of Washington and had evidence of residual enhancing tumor on T1 weighted images in the first post radiation MRI study. Upon examination of subsequent images and clinical interventions we found evidence of pseudo-progression in six of these patients. We created individualized models of tumor growth for these 28 patients and computed their "Days Gained" score - a measure of deflection of actual tumor growth from the model-predicted untreated tumor burden. RESULTS: Based on a reporter-operator curve, we found that 104 Days Gained was an optimal discriminating cutoff (AUC = 76.1%). We found that all patients with pseudo-progression (n = 6) had Days Gained scores of 104 or above, with an odds ratio of 5.5 (p = 0.03). None of the patients with Days Gained scores less than 104 (n = 11) had pseudo-progression. There was no significant difference between the patients with greater than 104 Days Gained and no pseudo-progression (n = 11) and those who had pseudo-progression. Additionally, patients with a higher Days Gained score had a longer predicted survival (median 610 vs. 376 days, p = 0.04). CONCLUSIONS: Our novel method for measuring the predicted impact of treatment on both diffuse and proliferative tumor burden for glioblastoma discriminates those patients who are likely to have true progression on their first post treatment scan. While we anticipated that patients with pseudo-progression would have the lowest estimate of Days Gained due to nonspecific imaging changes, we find instead that these patients are indistinguishable from the longterm responders. This difference in Days Gained may indicate that there is a robust biological response underlying the patients with an increased survival probability that is the subject of further investigation.

P.172. KNOW THY ENEMY: EXPLOITING INTER-TUMORAL HETEROGENEITY TO INFORM TREATMENT DESIGN

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The last 50 years have delivered only modest progress in the treatment of glioblastoma, as the median prognosis has not changed significantly. We propose that a patient-specific understanding of disease kinetics may provide a useful and novel tool in the war against glioblastoma. Specifically, we believe that there are paradoxes in tumor growth and response to therapy that can be exploited and used against the tumor enemy. Initially, patient-specific mathematical model for glioblastoma growth and invasion were generated for 35 patients and revealed that although about two-thirds of the patients survived relatively long times, only about half of these can be attributed to their treatments. In other words, the other half did not survive longer than would be predicted from their rates of growth if not treated. This seeming contradiction helps to explain two common paradoxes seen in tumor treatment response: 1) some tumors show a significant response to treatment on imaging, but the patient survival time is not very different than the average (fast growing tumors), and 2) some tumors show almost no response to treatment, but patient survival times still remain average (slow growing tumors). To confirm the practical utility of these paradoxical observations, we have generated similar patient-specific simulations in a broader cohort of patients and quantified the extent to which therapy delayed their tumor growth, a response metric we have termed "Days Gained." This metric has been proven to be predictive of not only overall survival but also time to progression ($p < 0.01$). These analyses certainly suggest that the treatment of glioblastomas as a single homogeneous group without respect to patient-individualized rates of growth or invasion should obviously be reconsidered. To exploit the patient-to-patient variation in tumor kinetics quantified by these techniques, we propose a patient-individualized treatment design that is informed by these kinetics. Indeed, as these individual growth rates have been shown to be directly proportional to the tumor level of radiation sensitivity (Rockne et al, 2010) this provides an opportunity to stratify patients into optimized radiation treatment plans that exploit the patient-specific radiosensitivity providing an opportunity for improved outcomes that should be tested in multi-center clinical trials.

P.173. CALCIUM-ACTIVATED POTASSIUM CHANNELS: A POSSIBLE TARGET FOR THE PHARMACOLOGICAL TREATMENT OF GLIOBLASTOMA

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Astrocytomas represent 80-85% of all gliomas and among them the glioblastoma multiforme (GBM) is the most malignant brain tumor of the adult brain. One peculiar aspect of these tumor cells is their ability to invade the surrounding normal brain parenchyma, preventing also the positive outcome of surgical resection. The activation of ion channels is crucial during cell movement, including glioblastoma cell migration during the invasion of normal brain parenchyma. We have previously described the contribution of calcium-activated potassium channel (KCa3.1) activity in the chemotactic response of glioblastoma cells to CXCL12; a chemokine whose expression in glioblastoma has been positively correlated with its invasive capacity. We show, *in vivo*, the involvement of KCa3.1 in glioblastoma invasiveness: when severe combined immunodeficient mice are injected with human GBM cells and treated with a specific inhibitor of KCa3.1, TRAM-34, a reduced tumoral area was observed. More over treated mice showed a reduced astrocyte activation and a prolonged survival time in comparison to controls. These data indicate KCa3.1 as a good candidate for the pharmacological treatment of malignant brain tumors.

P.174. COMPARISON OF TWO PALLIATIVE RADIOTHERAPY REGIMENS IN POOR PROGNOSIS PATIENTS WITH GLIOBLASTOMA MULTIFORME

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INTRODUCTION: The outlook for elderly and/or frail patients with glioblastoma multiforme (GBM) deemed not fit enough for standard chemoradiotherapy is very poor. Currently, it is standard practice to use hypofractionated radiotherapy alone, although trials of combine modality therapy are underway. At our centre we typically prescribe 30Gy/6#, but we consider an alternative more aggressive regimen of 45Gy/20# (in-patient twice daily treatment over 2 weeks) in fitter patients. METHOD: The radiotherapy planning system at the Beatson West of Scotland Cancer Centre was interrogated to identify GBM patients who were prescribed a radiation dose of 45Gy/20# or 30Gy/6# between January 2001 and December 2010. Data was analysed in SPSS v20. RESULTS: 147 patients were identified over a 10-year period. All but 2 patients had a confirmed histological diagnosis of GBM. 89 patients (60%) received 30Gy/6# and 58 patients (40%) received 45Gy/20#. Treatment compliance was over 90% and toxicity rates were comparable. Despite the higher rate of debulking surgery as opposed to biopsy in the 45Gy/20# group compared with the 30Gy/6# group (65% vs 42%, p = 0.008), there was no difference in median survival (5.4 months vs 5.2 months, p = 0.281). However, 1-year survival was better in the 45Gy/20# arm (20% vs 6%). There was no statistically significant difference in performance status, median age (68 vs 65.5 years, p = 0.896) or field size (9.0 x 9.5cm vs 8.8 x 8.9cm, p = 0.771) between the two groups suggesting that selection of patients based on fitness is very

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subjective. CONCLUSION: Similar results were observed with two different dose/fractionation protocols in the palliative management of elderly and/or frail patients with GBM. Given the standard dose of 30Gy/6# has the advantage of fewer fractions and avoids a hospital stay, this is the treatment of choice for the majority of patients.

LOW GRADE GLIOMAS

P.175. A LARGE CEREBELLAR GANGLIOGLIOMA WITH AN EXTRA AXIAL COMPONENT IN A YOUNG PATIENT: A CASE REPORT

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BACKGROUND: Gangliogliomas are uncommon braintumours and infratentorial presentation is rare. We present a unique case of a large, cerebellar ganglioglioma in a young patient. Clinical presentation: A 22-year old male presented with recent complaints of headaches and vision loss. His medical history was uneventful. INTERVENTION: A suboccipital craniotomy was performed and the tumour was gross totally removed. CONCLUSIONS: Although cerebellar gangliogliomas are rare, they should be considered in the differential diagnosis, especially in children and young patients.

P.176. BEVACIZUMAB ALONE OR IN COMBINATION WITH IRINOTECAN IN RECURRENT WHO GRADE II AND GRADE III GLIOMAS

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The repertoire of salvage regimens for patients with WHO grade II and III gliomas recurring or progressing after surgery, radiotherapy and temozolomide chemotherapy, is limited. Based on promising response and progression-free survival (PFS) data in recurrent glioblastoma, the use of bevacizumab (BEV) has been extended to recurrent grade II/III gliomas. We here report on the safety and efficacy of BEV alone or in combination with irinotecan in 39 patients with recurrent grade II/III gliomas. Both, BEV monotherapy and its combination with irinotecan were well tolerated. Response rates were 26% as monotherapy and 33% in combination as assessed both by MacDonald criteria and by RANO criteria. Median PFS was 4.2 months, and the PFS rate at 6 months (PFS-6) 29%, for BEV alone, and 4.7 months and 42% for the combination. Median PFS and PFS-6 were 4.2 months and 32% for all patients with grade II tumors and 4.9 months and 35% for all patients with grade III tumors. The median overall survival (OS) was 14.8 months for BEV alone and 8.1 months with BEV plus irinotecan, and 9.9 months for grade II and 14.8 months for grade III tumors. Outcome after failure of BEV was better when patients continued BEV beyond progression. BEV has limited activity in recurrent WHO grade II/III gliomas, the additional value of irinotecan remains questionable. Prospective studies with BEV-free control groups are required to better define the role of BEV among the limited therapeutic options in patients with recurrent WHO grade II/III gliomas.

P.177. TWO CASES OF ASTROBLASTOMA IN YOUNG FEMALES WITH DIFFERENT CLINICAL BEHAVIOUR

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INTRODUCTION: Astroblastoma is a rare mostly supratentorial glial tumor occurring predominantly in children and young adults with a strong female preponderance. Due to the rarity with only about 120 cases described so far, treatment strategies are still to be discussed. We describe two more cases to add to the experiences with this tumor entity collected so far. Case 1: A 24-year old female presented with a four weeks history of severe headache, vomiting and focal seizures affecting her left arm. Cranial CT and MRI scans showed a right temporal meningeal based partly cystic tumor with perifocal edema. Intraoperatively, the tumor showed dural and bony invasion but was otherwise well demarcated. It could be removed macroscopically completely. Histology gave the result of high grade astroblastoma. After referral to a neighbouring Tumor Centre, decision was made against chemo- or radiotherapy. MRI scans six months postoperatively showed no recurrence. The patient refused further MRI controls but had developed no clinical signs or symptoms when last seen four years postoperatively.Case 2: A sixteen-year old female presented with a six months history of intermittent headache, dizziness, and nausea. Cranial MRI scans revealed a left parietooccipital mass with heterogeneous bubbly contrast enhancement. Intraoperatively, the tumor was only partly well demarcated but macroscopically, tumor removal was complete. Histology gave the diagnosis of low grade astoblastoma. MRI scans 3, 6, and 9 months postoperatively showed a slowly growing recurrent tumor which was removed and again was diagnosed as low grade astroblastoma. Due to the early local recurrence, the patient received radiotherapy. Two years later, MRI showed no tumor in the former tumor bed but a meningeally based tumor nodule slightly more frontal. After removal, histology again gave the result of low grade astroblastoma.CONCLUSION: Our two cases on the one hand show the typical features of astroblastoma. Both were young females with supratentorial mass lesions showing typical radiological and histological characteristics of astroblastoma. On the other hand, the patient with high grade astroblastoma showed no clinical recurrence four years after tumor removal without receiving radiotherapy, while the patient with the low grade tumor developed early recurrence as well as a second tumor localization. Therefore, these cases illustrate well the unpredictable clinical behaviour of the tumor with the need to collect as many cases as possible to determine optimal treatment strategies for the future.

P.178*. MOLECULAR CLASSIFICATION OF LOW GRADE, ANAPLASTIC GLIOMAS AND THEIR DERIVATIVES BASED ON WHOLE GENOME MICRORNA PROFILING

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Previous successful molecular subtyping systems are focused on primary glioblastoma (GBM) which have entirely different genetic background and cell origin from other kinds of glioma. To date, no systematic molecular classification were reported on low grade, anaplastic gliomas and their derived secondary GBMs which have similar genetic background. and cell origin and are potential different stages of malignant progression. In this study, we analyzed miRNA expression profiles from 116 glioma samples including low grade, anaplastic gliomas and secondary GBMs, identifying three subgroups: A, O and M subtypes. Majority of samples in A subtype were astrocytomas. Most oligodendrocytomas were in O subtype which was characterized by high frequencyof 1p/19q LOH and enrichment with oligodendrocyte miRNA signature. Samples in M subtype are all anaplastic gliomas and secondary GBMs and with higher Ki-67 expression. Of note, nearly 50% astrocytomas were assigned into O subtype and characterized by oligodendrocytoma characteristics such as 1p/19q LOH and better clinical outcome when compared with those in A subtype. These results indicated that our classification scheme could identify a subset of. astrocytomas with oligodendrocytoma characteristics. ROC analysis showed that let-7s were potential diagnostic markers for astrocytomas. with oligodendrocytoma characteristics. Further, let-7s could also identify a. subpopulation of oligoastrocytomas with oligodendrocytoma characteristics in an independent validation cohort. Taken together, our findings firstly report a novel classification system of glioma based on miRNAs and identify astrocytomas with oligodendrocytoma characteristics which may provide new directions for clinical treatments of low grade gliomas.

P.179. A CASE-CONTROL STUDY ON OCCUPATIONS IN DIFFUSE GRADE II ADULT GLIOMA PATIENTS

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BACKGROUND: Diffuse WHO grade II gliomas (oligodendroglioma, diffuse astrocytoma and oligoastrocytoma, grade II) are rare tumors

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(incidence ≤ 1/100,000 person-years) [1], and differ from the other gliomas in terms of clinical and radiological presentation and evolution [2]. Except from few cases, their cause remains unknown. To date, most epidemiological studies have investigated all grades of gliomas and specific studies are rare. In particular, there is, to our knowledge, very few specific data concerning occupations and environmental exposures in adult diffuse grade II glioma patients. MATERIALS AND METHODS: We conducted a retrospective case-control study on histologically confirmed diffuse WHO grade II glioma adult patients, diagnosed in one of three French neurosurgical centers (Montpellier, Nancy and Paris Lariboisière hospitals). Questionnaires were established for this study and sent to patients and controls. Education level, job history, occupations (leisure and physical activities) and sleep data were collected and analyzed. RESULTS: Statistical analysis is ongoing. We will present detailed data for 215 patients and 450 controls. CONCLUSIONS: This study is, to our knowledge, the first one to specifically investigate professional and leisure occupational data in diffuse WHO grade II adult glioma patients.

P.180. MOLECULAR AND FUNCTIONAL CHARACTERIZATION OF MIR-137 IN OLIGODENDROGLIAL TUMORS

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MicroRNAs are short non-coding RNAs that function as key regulators of diverse cellular processes through negative control on gene expression at the post-transcriptional level. A paper reported (Silber et al., BMC Med 2008;6:14) that miR-137 expression was diminished in anaplastic astrocytomas and glioblastomas. The aims of this study were to investigate whether miR-137 was involved in oligodendroglial tumors and to elucidate the biological functions of miR-137 in gliomagenesis. Quantitative RT-PCR analysis revealed that miR-137 was significantly downregulated in 17 of 20 (85%) oligodendrogliomas and 16 of 16 (100%) oligoastrocytomas examined compared to normal brain tissues ($p < 0.05$). Ectopic expression of miR-137 inhibited cellular proliferation and induced apoptosis in oligodendroglioma and glioblastoma cells. To identify miR-137 targets, a computational approach was employed for target prediction. One of the candidate genes, CSE1L (chromosome segregation 1-like), was found to be downregulated at protein but not at mRNA level upon miR-137 overexpression. Luciferase reporter assay showed that miR-137 could interact with the putative miR-137 binding site in the 3' untranslated region of CSE1L, but not with a mutated miR-137 binding site. These results strongly suggest that CSE1L is a target of miR-137. Immunohistochemical analysis further demonstrated that CSE1L was overexpressed in oligodendroglial tumors. Moreover, knockdown of CSE1L by RNA interference led to reduced proliferation and induced apoptosis in glioma cells. These effects were similar to those observed after miR-137 overexpression, but to a lesser extent, suggesting that miR-137 may mediate its effects partly through CSE1L. CSE1L has been implicated in cellular proliferation and apoptosis, and is involved in modulating expression of a subset of p53 target genes. In conclusion, our results demonstrate that miR-137 deregulation is common in oligodendroglial tumors and suggest that the miR-137/CSE1L axis may represent a potential therapeutic target for treatment of oligodendroglial tumors.

P.181. AMINO ACID PET IN NON-ENHANCING LOW-GRADE GLIOMAS: CHALLENGING THE DURATION OF CHEMOTHERAPY

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BACKGROUND: MRI responses during chemotherapy (CTx) of non-enhancing low-grade glioma WHO II (LGG) may occur with delay and even after discontinuation of CTx. This may lead to overtreatment if CTx is administered MRI-guided. Assuming that metabolic responses precede MRI responses, we therefore characterized CTx response using amino acid positron emission tomography (PET) and MRI to determine response onset and stabilization. PATIENTS AND METHODS: Ongoing retrospective multicenter study on progressive or recurrent non-enhancing LGG. No patient received previous radiation therapy. Temozolomide CTx was administered according to local policy for either 12 months or until progression/toxicity (5/28d, 21/28d, 7/14d or 5/7d regimen). Amino acid PET (either F-18 tyrosine or C-11 methionine) and standard MRI studies were performed prior to and at regular follow-up intervals during CTx. The active tumor size on PET images was defined as the volume of pixels exceeding 110% of cerebellar tracer uptake. On MRI the tumor size was assessed from T2-weighted images. Response on PET and MRI was defined as a size decrease of ≥ 10% from baseline. Response stabilization was achieved if the difference in size did not exceed 10% between subsequent scans. RESULTS: 26 patients with astrocytic (11) or oligodendroglial (15) supratentorial tumors were studied (mean age 48 yrs). 15 responders were identified. Onset of PET response was observed as early as 2 months after initiation of CTx and followed a mono-exponential time course. Initial MRI responses were observed after 5 months. At 6 months response leveled at 42% of baseline for PET and at 87% for MRI. Response stabilization on PET was observed 6 to 14 months earlier as compared to MRI. 15 patients progressed at a mean of 38 months after initiation of CTx which was completed as scheduled in eight, and terminated due to progression or toxicity in seven patients. In these patients the total administered dose and duration of CTx did not correlate with the progression-free survival (PFS). INTERPRETATION: If shorter courses of CTx are not inferior to CTx given until tumor progression in terms of PFS the stabilization of a metabolic response may determine the individual duration of CTx. Amino acid PET could assist to avoid overtreatment imposed by any CTx duration recommended as 'standard', and to reduce the incidence of CTx-associated adverse events.

P.182. BEVACIZUMAB TREATMENT IN RECURRENT ADULT BRAINSTEM GLIOMA

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BACKGROUND: Brainstem gliomas (BSG) in adults are rare diseases whose treatment relies on radiotherapy. In recurrent tumors, the effectiveness of antiangiogenic treatment is not established despite a few encouraging case reports. PATIENTS AND METHODS: We retrospectively reviewed data from all patients of our institution who fulfilled the following criteria: i) Histologic or MRI diagnosis of BSG; ii) recurrent tumor after failure of radiotherapy and of at least one line of chemotherapy; iii) treatment with at least 2 courses of bevacizumab (10 mg/kg IV Q 2 weeks); 4) Monthly MRI follow up with clinical evaluation every 2 weeks. Response was evaluated according to the RANO criteria. RESULTS: Between December 2008 and August 2011, eight patients fulfilled the inclusion criteria. There were 5 men and 3 women. Median age was 38 years (range 25-54). Tumor histology was obtained at diagnosis in 6 patients (4 low-grade oligodendrogliomas, 1 low-grade mixed oligoastrocytoma and 1 anaplastic astrocytoma) while 2 had a MRI diagnosis of diffuse infiltrating intrinsic glioma. In addition to radiotherapy, all patients had failed temozolomide as first line chemotherapy and 4 had failed second line chemotherapy (nitrosourea-based in 3 and carboplatin in 1). The response rate to bevacizumab according to RANO criteria were 4 PD, 3 SD (6, 10 and 14 weeks), and 1 PR (but in this case bevacizumab was interrupted at 4 weeks because of intestinal perforation). Median progression-free survival (PFS) was 1.4 months and median overall survival (OS) after bevacizumab therapy was 3.5 months (1.2-6.4 months). OS was not influenced by KPS, age at the onset of treatment or initial histology. At progression (bevacizumab failure), 4 patients had a substantial reduction of T_1/gadolinium enhancement despite increasing lesions on T_2/FLAIR sequences and clinical deterioration, a feature underlining the importance to use RANO criteria. Treatment-related side effects were grade II thrombopenia in 2 patients, high blood pressure in 1 and intestinal perforation in 1. CONCLUSION: The benefit of bevacizumab appears quite modest in adults with recurrent brainstem gliomas as compared to recurrent supratentorial gliomas.

P.183. RADIATION THERAPY IN LOW-GRADE GLIOMAS: A DOSIMETRICAL COMPARISON BETWEEN INTENSITY-MODULATED PHOTON AND PROTON THERAPY

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AIM: To explore the potential dosimetrical benefits of intensity-modulated proton therapy (IMPT) with respect to intensity-modulated photon radiation therapy (IMRT) in patients (pts) with low-grade gliomas (LGG). METHODS: Six pathologically confirmed (one left occipital, two left and one right temporal,

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one left parietal, and one right frontal), previously irradiated LGG pts were retrieved and re-planned both with IMRT and IMPT. Planning computed tomography and magnetic resonance images (MRI) were co-registered to properly define organs at risk (OARs) and planning target volume (PTV). PTV was represented by surgical cavity, any contrast-enhancing area on post-gadolinium T1-weighted MRI as well as hyperintensity on T2-weighted MRI plus 2.5 cm expansion. Contours were manually edited to respect natural anatomical barriers. The dose prescription was 54 Gy in 27 fractions with the following goals: firstly, compliance of maxDose constraints for primary OARs (optic nerves, chiasm, retinas, brainstem); secondly, volume receiving 95% of the prescribed dose (V95) $\geq$ 99% for PTV. Once the previous goals were met, a further effort was made to reduce the dose to secondary OARs: cochlea meanDose, lens maxDose, pituitary gland volume receiving 50 Gy (V50), brain (whole brain tissue minus PTV) and temporal lobes (omolateral lobe = whole lobe minus PTV) volume receiving 30 (V30) and 40 Gy (V40). Target conformity was evaluated by the means of conformity index. Wilcoxon's matched pair's test was performed to determine statistical differences between the techniques and $p < 0.05$ was considered significant. RESULTS: Both techniques always fulfilled the established constraints for primary OARs. IMPT and IMRT provided same target coverage and conformity. With few exceptions, IMPT systematically provided a lower maxDose to primary OARs with respect to IMRT: average reduction was 1.8 Gy for chiasm, 4.6 Gy for omolateral optic nerve, 11.1 Gy for contralateral optic nerve, 8.8 Gy for brainstem, 5.3 and 11.6 Gy for omo- and contralateral retina, respectively. All but contralateral optic nerve figures were not statistically significant. IMRT and IMPT achieved same results regarding pituitary gland V50. IMPT significantly reduced the maxDose to omo- and contralateral lens as well mean dose to contralateral cochlea but not to the omolateral one. Moreover, IMPT scored significantly better results in terms of V30 and V40 for both brain (mean reduction, 11.4% and 4.5%, respectively) and omolateral temporal lobe (average reduction, 28.3% and 21.1%, respectively). It did the same for contralateral temporal lobe V30 (mean reduction, 5.6%) but not V40. CONCLUSIONS: IMRT and IMPT provide same target coverage and primary OARs sparing in LGG pts receiving a standard irradiation regimen. IMPT achieves a significant better sparing of secondary OARs. The healthy brain and temporal lobes sparing could be clinically meaningful.

P.184. A TUMOR GROWTH INHIBITION MODEL FOR LOW-GRADE GLIOMA TREATED WITH CHEMOTHERAPY OR RADIOTHERAPY

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PURPOSE: To develop a tumor growth inhibition model for adult diffuse low-grade gliomas (LGGs) able to describe tumor size evolution in patients treated with chemotherapy or radiotherapy. EXPERIMENTAL DESIGN: Using longitudinal mean tumor diameter (MTD) data from 21 patients treated with first-line PCV chemotherapy, we formulated a model consisting of a system of differential equations, incorporating tumor-specific and treatment-related parameters, that reflect the response of proliferative and quiescent tumor tissue to treatment. The model was then applied to the analysis of longitudinal tumor size data in 24 patients treated with first-line temozolomide chemotherapy and in 25 patients treated with first-line radiotherapy. RESULTS: The model successfully described the MTD dynamics of LGG before, during and after PCV chemotherapy. Using the same model structure, we were also able to successfully describe the MTD dynamics in LGG patients treated with temozolomide chemotherapy or radiotherapy. Tumor-specific parameters were found to be consistent across the three treatment modalities. CONCLUSIONS: Using MTD data, we propose for the first time a tumor growth inhibition model able to describe LGG tumor size evolution in patients treated with chemotherapy or radiotherapy. In the future, this model might be used to predict treatment efficacy in LGG patients and could constitute a rational tool to conceive more effective chemotherapy schedules.

P.185. CHORDOID GLIOMA OF THIRD VENTRICLE: CASE REPORT AND REVIEW OF LITERATURE

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BACKGROUND: Chordoid glioma is a rare tumor (WHO grade 2) with both glial and chordoid features located in third ventricle or suprasellar region. It represents a new clinico-pathological entity occuring in adults with female predominance. 51 cases are reported in the literature. We report a case and focus on radiological characteristics and pathological morphology. Case report. A 31-year-old male presented to emergency unit with severe headaches, nausea and paresthesia of right arm for 2 weeks. Family had noted some behavioural changes. CT scan shows an hypodense mass in the third ventricle with hydrocephalus. The center of the lesion is slightly hyperdense. Magnetic resonance imaging scan revealed an oval well-circumscribed heterogeneous mass (23 x 38 x 32 mm) with slight oedema in the adjacent right thalamus. The tumor was hypoointense on T1 and hyperintense on T2. The mass didn't enhance heterogeneously after Gadolinium administration. The center of the lesion was hyperdense on CT, isointense on T1 et hypointense on T2 compatible avec acute hemorrhagic content. A diagnosis of ependymoma or subependymoma was suggestedacute hydrocephalus secondary to obstruction of the posterior part of the third ventricle by a 4cm well-delineated spheric tumor. A cisternoventriculostomy combined with a biopsy was performed and alieviated the increased intracranial pressure. MRI showed the tumor was slightly enhanced by contrast in its center and did not invade right the thalamus. No cyst was associated. A subtotal resection was achieved through a right transfrontal inter-thalamo-trigonal route. The tumor appeared as a soft grey lesion suggesting a pilocytic glioma. Postoperatively, headaches disappeared but memory troubles remained. Microscopically,the tumor was well difined non infiltrating composed of epitheliod cells with abundant cytoplasm with vacuole and round nucleoli, branching capillaries. The cells were poorly immunopositive for GFAPand the Ki67 was low (<1%). CONCLUSION: We discuss a case of clinical typically chordoid glioma of the third ventricle with some radiological and pathologic characteristics and review of literature.

P.186. INSULAR GLIOMA COMBINED TREATMENT: A RETROSPECTIVE ANALYSIS OF 50 CONSECUTIVE PATIENTS

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INTRODUCTION: Insular gliomas are peculiar due to the complex anatomy of this region, being crucial for both motor and language systems. By analyzing the present series we aimed at assessing: i) our approach to radical resection; ii) the volumetric extent of resection (EOR); iii) the morbidity profile; iv) the impact on outcome; v) the effect of the combined surgical and chemotherapeutical treatment. PATIENTS AND METHODS: A retrospective review of prospectively collected data was performed. WHO grade II to IV lesions, were volumetrically analyzed on FLAIR and gadolinium-enhanced-T1-weighted MRI, respectively. Surgery was performed according to functional boundaries. Intraoperative mapping and monitoring procedures and Neuronavigation were employed in all cases. Neuropsychological monitoring was adopted in patients under asleep-awake anaesthesia. A post-operative volumetric MRI were performed within 24-48 hours since surgery. EOR was accounted as previously described. Patients were submitted to TMZ-based chemotherapy (either standard or dose-dense regimen pre- or post-operatively). RESULTS: Mean age was 41 years ($\pm$13, 18 ÷ 68), with 35 males, and 15 females. All but 2 patients had right-hemisphere dominance. Seizures occurred in 30%, 8% and 28% of patients as simple, simple with secondary generalization and generalized seizure; 9% patients had headaches, 7% of cases were incidental, 6% had language disturbances and 12% had vague neurological symptoms leading to a MRI study performance. Left insula was involved in 76% of patients. Pure frontal and temporal lobe extension were seen in 38% of patients, while 20% had fronto-temporal lesion simultaneous involvement. Mean pre-operative lesion volume was 59.4 ml ($\pm$32.3, 9.3 ÷ 124.6 ml). Asleep-awake anaesthesia were employed in 60% of patients, while asleep regimen was adopted in the remaining. In 48% of patient an EOR greater than 80% was reached, in 25% of patients and EOR between 50-80% was reached. According to WHO classification, grade II, III and IV glioma were encountered in 60, 28 and 12% of patients. Transient neurological impairment, fully resolving within 3 months since surgery, occurred in 85% of patients. Seizure control (Engel I) was achieved in 60% of patients and correlated with EOR. Chemotherapy was performed in adiuvant treatment (6-14 cycles, mean 9) in those with partial EOR (28% patients) and resulted in a reduction or stabilization of the tumour mass allowing further complete resection in 78% and a seizure control (Engel I) in 93% of patients of this subgroup. CONCLUSIONS: The surgical treatment of insular gliomas is an effective option for addressing gliomas harboured in this eloquent region, where a greater EOR can be pursued with a low morbidity profile and a seizure control. Combined surgical and chemotherapeutic treatment improved disease control in those patients with partial resection.

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P.187*. REGARDLESS OF THE MOLECULAR STATUS, NEOADJUVANT CHEMOTHERAPY CAN OPTIMIZE THE EXTENT OF RESECTION OF WORLD HEALTH ORGANIZATION GRADE II GLIOMAS

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INTRODUCTION: Diffuse low-grade gliomas (DLGGs) frequently involve eloquent areas, precluding, in some cases, a total/subtotal surgical removal. Among other options, neoadjuvant chemotherapy can be offered to these patients. Its feasibility and functional tolerance (cognition and quality of life) have been demonstrated. OBJECTIVE: The aim of the present study is to assess the clinical and radiological impact of this strategy on the natural history according to the molecular status. METHODS: We retrospectively selected seventeen patients considered at diagnosis or recurrence as "non operable" (because of a functional areas infiltration or a too large contralateral extension) and who underwent temozolomide based chemotherapy inducing tumor volume decrease immediately followed by a maximal surgery. RESULTS: The median follow-up since the initial radiological diagnosis was 5.9 years (range 1.4 to 11). The seventeen patients were still alive. 1p19q codeletion was identified in six patients, IDH mutation and MGMT promoter methylation in twelve patients, both 1p19q codeletion and IDH mutation in five patients. Median time to malignant transformation was 5.9 years (mean 5.6; range 1.4 to 11). Age, 1p19q, IDH and MGMT promoter status had no impact on time to malignant transformation. Chemotherapy reduced tumor volume (median -35.6%, range -61.6% to -5.1%) in contralateral hemisphere through the corpus callosum in seven cases (41%) and in ipsilesional functional areas in ten cases (59%). Chemotherapy significantly decreased the VDE with a median of -3.2 mm/year (range, -29.8 to -0.9 mm/year) as compared to VDE before chemotherapy (median 3.7 mm/year; range 1.2 to 19.2 mm/year) ($p < 0.001$), independently of 1p19q, IDH and MGMT status. Surgery was performed 5.6 months after the end of chemotherapy (median, range 1.2 to 28). The median extent of resection was 92.9% (mean, 92.6%; range 85.5% to 100%) and the median postoperative residual tumor was 4cc (mean, 4.9; range 0 to 20cc). A tumor volume decrease of more than 20% was correlated with a lower postoperative residual tumor (median 2 cc, $p = 0.04$), a greater extent of resection (93.1% versus 89.5%) and a better prognosis ($p = 0.04$). Total removals were observed only in the subgroup with a volume decrease of more than 20%. CONCLUSION: Regardless of the molecular status, neoadjuvant chemotherapy can optimize surgical resection of DLGGs and could have an impact on their natural history. Further prospective studies with a larger effective are needed.

P.188. RE-IRRADIATION OF RECURRENT GLIOMA: EFFECT ON TUMOR CONTROL AND COGNITIVE FUNCTION

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PURPOSE: to retrospectively assess the effectiveness of renewed radiation therapy and its influence on the cognitive function of glioma patients. PATIENTS AND METHODS: 20 patients with recurrent glioma (12 astrocytoma, 3 oligodendroglioma, 1 anaplastic astrocytom, 3 glioblastoma), were treated; 21/22 recurrences were in-field, 1/22 was out of field. A median dose of 32 Gy (range 30-42 Gy) in fractions 1,6-1,8 Gy/d x 5d and 4 weeks by Varian LINAC. Six patients received temozolomide ($75mg/m^2$) and re-irradiation. Patients were subjected for cognitive testing 6 months and 1 year after re-irradiation. RESULTS: Re-irradiation was well tolerated. Fourteen of 22 were reoperated at recurrence before re-irradiation, the tumor grade was generally higher for recurrent astrocytoma, the same grade for oligodendroglioma and glioblastoma. Time from first irradiation ranged from 4-10 years in astrocytoma and oligodendroglioma, 6 months to 4 years for glioblastoma. With a current median follow-up of 1 year (range 6 mo-2 years) after re-irradiation, 2 pat have died of tumor progression (malignified astrocytoma). The Cognitive function was not altered after re irradiation. When there was a decline of cognitive function, it was related to already declining function due to tumor localisation and progression before intervention. CONCLUSION: Re-irradiation is a safe option for treatment of recurrent glioma. Timing is important: not to wait to long when recurrence is diagnosed, as re-irradiation, even if it can control the tumor evolution, is not able to restore the neurologic and cognitive deficit.

P.189. POSTOPERATIVE RADIOTHERAPY IN PATIENTS WITH PLEOMORPHIC XANTHOASTROCYTOMA

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BACKGROUND: Pleomorphic xanthoastrocytoma (PXA) is a very rare variant of cerebral glioma. W literaturze medycznej ostatnich 25 lat opisano około 300 przypadków tego nowotworu. It is characterized by quite good prognosis with 10-years relapse free survival and overall survival of 61% and 70%, respectively. It occurs primarily in young adults and looks like a superficially laying cyst located mainly in temporal and occipital lobe. Histologic examination usually reveals atypic cells, increased mitotic index and presence of necrosis (increased mitotic index and necrosis are recognized prognostic factors). The basic treatment modality for PXA is surgical resection and the extent of surgical resection is the major prognostic factor. The role of adjuvant radiotherapy and chemotherapy is not well established. Radiotherapy with total doses of 30 - 60 Gy is recommended in patients after subtotal resections and in those who have malignant variant of PXA. Chemotherapy is not used as a routine procedure. MATERIAL AND METHODS: Between 2000 and 2011 in the Oncology Center in Kracow 10 patients with PXA underwent postoperative radiotherapy. The group consisted of 6 women and 4 men with median age of 37 yeras (range from 28 to 50). Three patients underwent total and 7 subtotal resection of the primary tumor. Localisation of the primary tuomor was: temporal lobe - 4 patients, frontal lobe - 3 patients, parietal lobe - 2 patient, thalamus - 1 patient. All patients received conventionaly fractionted radiotherapy to the total doses of 50-60Gy. RESULTS: Four patients who underwent subtotal resection and had unfavorable prognostic factors (necrosis revealed in histopathologic examination, high mitotic index - ≥ 5) developed progresion and died within 3 years from diagnosis. The rest 6 patients are alive without progression. Three of them underwent subtotal resection but they had favorable prognosic factors (no necrosis in histopathologic examination, low mitotic index - <5). The most favourable prognostic factor was the type of surgery. The best prognosis had the patients after total resection. CONCLUSION: Literature data and our own experience does not allow the unambiguous definition of the role and place of the adjuvant treatment of PXA. Because of small number of patients and the slow growth of PXA it is difficult to clearly answer the question to what extent the good treatment outcomes are the result of the natural course of PXA, and what is involved in the adjuvant treatment.

P.190. LOW-GRADE GLIOMAS: THE CLEVELAND CLINIC EXPERIENCE

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BACKGROUND: Low-grade gliomas account for 10-20% of all primary brain. tumors. There is limited data on specific prognostic factors for patients. with low-grade gliomas. METHODS: After obtaining IRB approval, the Cleveland Clinic Brain Tumor and Neuro-Oncology Center's database was used to identify patients with histologically confirmed grade 2 glioma at the time of diagnosis. Multivariable analysis was conducted with use of a Cox proportional hazards model and a stepwise selection algorithm that used $p < 0.10$ as the criteria for entry and $p < 0.05$ as retention in the model to identify independent predictors of survival. RESULTS: Chart records of 478patients (54% of whom were men) diagnosed between 1991 and 2010 were included for analysis. The median age at presentation was 41 years (range, 18-83 years).42% of patients had biopsy only, 27% had gross total resection, 6% had near. total resection, and 25% had subtotal resection. 22% of patients were initially treated with radiation, 30% with adjuvant chemotherapy, and 7% with concurrent chemotherapy. Median progression free survival and median overall survival (OS) were 5.1 years and 12.8 years, respectively. On multivariate analysis, independent of additional therapy, five factors were identified as independent predictors of OS: age at diagnosis ($p = 0.002$), Karnofsky performance status (KPS, $p < 0.0001$), histology (astrocytoma vs. other, $p = 0.001$), hemispheric location (left or bilateral involvement vs. right, $p = 0.02$) and gender (male vs. female, $p = 0.0003$). CONCLUSIONS: Older age, male gender, poor performance status, astrocytic histology, and left hemispheric or bilateral involvement are associated with higher mortality.

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P.191. LONG-TERM FOLLOW-UP IN ADULT PATIENTS WITH LOW-GRADE GLIOMA (WHO II) POSTOPERATIVELY IRRADIATED. ANALYSIS OF PROGNOSTIC FACTORS

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BACKGROUND: There is little consensus about the optimal treatment for low-grade glioma (LGG), and the clinical management of LGG is one of the most controversial areas in neurooncology. Radiation therapy is one option for treatment of patients with LGG whereas other options include postoperative observation. The aim or this study is to report the long-term follow-up of a cohort of adult patients with LGG post-operatively irradiated in one institution, and to identify prognostic factors for progression free survival. MATERIAL AND METHODS: Between 1975 and 2005, 180 patients with LGG (WHO II) received postoperative irradiation after non radical (subtotal or partial) excision. Patients had to be 18 years of age or older, and have histologic proof of supratentorial fibrillary (FA), protoplasmic (PA) or gemistocytic astrocytoma (GA). Radiotherapy was given within 3 to 10 weeks after surgery. The treatment fields were localized and included the preoperative tumor volume, with a 1-2 cm margin, treated to a total dose of 50 to 60 Gy in 25 to 30 fractions over 5 to 6 weeks. RESULTS: Actuarial ten- year progression free survival (APFS) in the whole group was 19%. The worse prognosis was reserved for patients with GA. Ten-year APFS rates for GA, PA and FA were 10%, 18% and 22% respectively. CONCLUSION: The findings from our long-term cohort of 180 patients with LGG confirmed by uni- and multivariate analysis demonstrated that only astrocytoma histology significantly determined the prognosis. The best survival is reserved for patients with the fibrillary variant, and the worst for the gemistocytic one. KEY WORDS: low-grade gliomas, surgery, radiotherapy.

PEDIATRIC BRAIN TUMOURS

P.192*. CHARACTERISTICS OF FETAL BRAIN TUMORS WITH GENETIC ANALYSIS

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It is extremely rare that brain tumors are discovered at a fetal stage. Their pathological diagnosis is various and the treatment is not yet established. As for the malignant fetal brain tumors, they show rapid progress and the prognosis is very bad. We experienced six cases of brain tumors that were discovered by ultrasonic echo or MRI during 30-35 weeks at a fetal stage and we also used MRI for following them. Operation (biopsy: 3 cases, resection: 0 case) or autopsy was performed after birth and their pathological diagnoses were 2 cases of immature teratoma, and a case of primitive neuroectodermal tumor (PNET), congenital neuroectodermal tumor, desmoplastic infantile astrocytoma (with glioblastoma like components), hamartoma, each. All cases except hamartoma showed rapid growing and died within several weeks or months after birth. Because of their high intracranial pressure, 2 cases were forced to drain cerebrospinal fluid in emergency just after birth. Chemotherapy was done for 2 cases but they showed chemoresistance. We also analyzed genetic aberrations of these tumors by comparative genomic hybridization (metaphase CGH). Interestingly, they present none or little number of chromosomal aberrations within few weeks after birth, regardless of their malignancy. This result might suggest a difference between children and fetus about tumorigenic pathway with genetics. Fetal malignant brain tumors showed rapid growing and aggressiveness just after birth irrespective of pathological diagnosis. It seemed that there are some growing factors clinically and genetically at perinatal stage compared with general pediatric brain tumors, and their treatment and management are still difficult.

P.193*. IDH1 MUTATIONS WITH RELEVANCE TO 1P/19Q LOSS AND MGMT METHYLATION IN PEDIATRIC GLIOMA PATIENTS

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PURPOSE: Isocitrate dehydrogenase 1 (*IDH1*) mutations are genetic alteration with a high prevalence (50-70% of cases) in WHO grade II or III gliomas and secondary glioblastoma. The acquisition of *IDH1* mutations occurs early in the development of a glioma from a glial progenitor cell that can give rise to both astrocytes and oligodendrocytes. These results, however, are based on studies of adult gliomas, but not pediatric gliomas. In this study, we examined *IDH1* mutations in pediatric glioma patients with the following goals: (1) to compare the prevalence of *IDH1* mutations in pediatric gliomas with those of adult ones; (2) to evaluate the relationship between *IDH1* mutations and loss of 1p/19q or O^6-*methylguanine-DNA methyltransferase* (*MGMT*) promoter methylation. MATERIALS & METHODS: We analyzed the mutational hot spot, codon 132 of *IDH1* in 19 newly diagnosed pediatric gliomas treated in our hospital. Real-time PCR system followed by high-resolution melting (HRM) analysis were used to detect *IDH1* mutaions. We estimated loss of 1p/19q and MGMT methylation status by fluorescence *in situ* hybridization and methylation specific HRM, respectively. RESULTS: Of the 19 cases, *IDH1* was mutated in only one glioma (anaplastic astrocytoma). This case was accompanied with methylated *MGMT*. Four pediatric oligodendrogliomas with co-deletion of 1p/19q had no *IDH1* mutations and no methylated *MGMT*. CONCLUSIONS: The frequency of IDH1 mutations in pediatric gliomas was significantly low irrespective of tumor grades or histology. All 1p/19q co-deleted adult oligodendrogliomas showed *IDH1* mutations, whereas pediatric oligodendrogliomas did not. These results suggest that there is a difference between pediatric gliomas and adult ones in genetic significance of *IDH1* mutations in gliomagenesis.

P.194. PAX2 IS AN ANTIAPOPTOTIC MOLECULE WITH DEREGULATED EXPRESSION IN MEDULLOBLASTOMA

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PAX2 is a paired box transcription factor possessing a fundamental role in the embryogenesis of hindbrain and urinary tract. PAX genes are protooncogenes, PAX2 expression may contribute to the pathogenesis of renal cell carcinoma. Because of the expression of PAX2 and PAX5 in the developing hindbrain and their essential role in cerebellar development, it has been hypothesized that both genes may also be involved in medulloblastoma tumorigenesis. Although PAX5 is re-expressed in most medulloblastomas, we have previously shown that overexpression of Pax5 alone is not sufficient for medulloblastoma formation in mouse models. We here investigated the expression pattern of PAX2 and various genes of the neuronal lineage in medulloblastoma and glioma cell lines. We found high expression of PAX2 mRNA and PAX2 protein in medulloblastoma cells and some glioma cell lines independent of their neuronal lineage gene expression signature. Gene suppression of PAX2 decreased the expression of the PAX2 transcriptional target GDNF in Daoy cells and had a profound cytotoxic effect in vitro on Daoy medulloblastoma and T98G glioma cells. Expression of PAX2 was then assessed in two separate medulloblastoma tissue microarrays with a total of 61 patient samples by immunohistochemistry. PAX2 expression was detected in the majority of medulloblastoma samples and correlated with less differentiated histology. Therefore, PAX2 is a biomarker for a more aggressive medulloblastoma phenotype and may represent a novel therapeutic target.

P.195. HEADSMART BE BRAIN TUMOUR AWARE (HEADSMART): A GUIDELINE DEVELOPMENT AND DISSEMINATION STRATEGY TO SHORTEN SYMPTOM NTERVAL FOR CHILDREN PRESENTING WITH BRAIN TUMOURS IN THE UK

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INTRODUCTION: The RCPCH endorsed Brain Pathways Guideline for selecting patients for scanning with symptoms of brain tumour and the

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HeadSmart campaign (www.headsmart.org.uk) aim to reduce median symptom interval (SI) for UK children to 5 weeks, by enhancing public and professional awareness and offering web-based support for selection of children for scanning, observation or reassurance. The strategy was developed in response to:

- delays in diagnosis observed by specialists;
- media reports of delays;
- questions in the House of Commons;
- the All Party Parliamentary Group Manifesto (2010), which placed delays in diagnosis as its top action point.

AIMS: The HeadSmart campaign aims to reduce SI to a median of 5 weeks, to equal the best reported worldwide. It is supported by a decision support website, a Clinical Champions' network recording SI for newly diagnosed patients, and an evaluation programme; a health economic model is in development. METHODS: A literature review, meta-analysis of reported symptom intervals and a Delphi consensus process generated the Clinical Guideline which was endorsed by RCPCH (2005) and supported by other Colleges, accredited by NHS Evidence and is being considered within NICE Cancer Referral Guidance review. The dissemination strategy included:

- Survey of healthcare professionals' awareness of childhood brain tumours and the HeadSmart campaign
- Survey of public awareness of childhood brain tumours and the HeadSmart campaign
- Development of the HeadSmart website
- Presentation of guideline material at regional and national professional meetings
- Recruitment of clinical champions
- Media campaign - television, radio and facebook.

Concurrent government reports have prioritised timely diagnosis and access to treatment and justify prioritisation of children within health service developments. CONCLUSIONS: This is an attempt by specialists working with the public sector to influence children's health services for an important childhood condition. Should this strategy be selected as part of the international initiative.

P.196*. NEUROCOGNITIVE OUTCOME AND ACADEMIC ACHIEVEMENT IN ADULT SURVIVORS OF CHILDHOOD MEDULLOBLASTOMA

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PURPOSE: To investigate neurocognitive outcome and academic achievement in adult survivors of childhood medulloblastoma. PATIENTS AND METHODS: We assessed 51 adults (median age, 23.4, range 18-32 years) who were treated postoperatively for a medulloblastoma at Institute Gustave Roussy, with radiotherapy and/or chemotherapy between 1.4 and 15.3 years (median, 10.1). The last assessment was performed 2 to 17 years (median, 7.2) after radiotherapy. Clinical symptoms at diagnosis, postoperative neurological status, neuropsychological data, academic achievement and parental education were collected. RESULTS: Mean full scale Intellectual Quotient (FSIQ) at the last assessment was 81.6 (SD = 17.6); it was significantly lower in the 12 patients who experienced postoperative akinetic mutism (mean IQ = 69 vs 92, $p < 0.001$), but not related to the age at diagnosis ($p = 0.09$) nor the type of treatment they had received ($p = 0.1$). Moreover, the FSIQ was correlated to the parent's educational level ($p = 0.02$). Six survivors (11%) had severe intellectual disability, 20 (39.2%) were still studying, 14 (27.4%) had a regular employment and 11 (24.6%) were unemployed. Mean FSIQ for patients without any diploma, patients with National Vocational Qualification (NVQ) level 1,2, patients with NVQ level 3 and patients with upper level achievement were 70.8 (SD = 13.1), 83.1 (SD = 9.7), 82.9 (SD = 11.5) and 107.2 (SD = 18.0), respectively. CONCLUSION: We demonstrated that postoperative akinetic mutism and parental education were associated to the degree of cognitive impairment in adults treated for childhood medulloblastoma. The degree of academic achievement is strongly related to IQ scores.

P.197. EXTRAVENTRICULAR NEUROCYTOMA WITH MIB-1 LABELING INDEX OVER 10% IN A CHILD

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INTRODUCTION: Extraventricular central neurocytoma (EVN) is more unusual than central neurocytoma and is a distinct entity in the WHO 2007 guidelines. The terms "atypical neurocytoma"/"atypical EVN" have been coined for neurocytoma/EVN exhibiting MIB-1 LI >2% with/without anaplastic features and focal necrosis, vascular proliferation, and increased mitotic activity. Recent results achieved by Kane in the analysis of all reported intracranial EVN cases suggested that typical EVNs has a better prognosis than atypical EVNs after primary treatment, age younger 50 years is associated with a better prognosis than age equal to or greater than 50 years and there is a suggestion of trend for adjuvant external-beam radiotherapy to benefit subtotal resection in patients with EVNs, similar to the patients with atypical central neurocytomas. METHODS: The authors report a case of an 8-year-old girl presenting headache, vomiting, VI c.n. palsy and diplopia, mild disartria, left hemiparesis on admission, who was diagnosed an atypical extraventricular neurocytoma which exhibited a MIb-1 labeling index of > 10%. She underwent a total removal for the left fronto-temporal mass with full recovery of neurological deficit. RESULTS: Altough the atypical tumors are difined by MIB-1 index score >3% or by atypical histological findings, associated with poor clinical outcome, the MIB-1 LI appears to be the best predictor of proliferative potential and clinical outcome of central neurocytoma. In the case presented the authors observed the rare association between high MIB-1 LI (over 10%) and younger patient age. Nevertheless the patient was not subjected to adjuvant therapy and the short-term outcome was good. CONCLUSION: Given the limited information about extraventricular neurocytomas (EVN) in the literature and the absence of guidelines about the treatment for EVNs, the authors present a case of EVN treated with total surgical resection without following adjuvant therapy, making a contribution to the discussion about the development of the guide treatment decisions.

P.198. COMPLEX ESTIMATION OF THE PSYCHOLOGICAL WELL-BEING IN CHILDREN WITH THE BRAIN TUMORS UNDER DIFFERENT TYPES OF TREATMENT.

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BACKGROUND: The effectiveness of the children brain tumor treatment increased in recent decades. Nevertheless children with the head brain tumors are supposed to have serious limitations in their development. There is need of elaboration of the psychologically based criteria of the estimation of psychological well-being - cognitive, emotional development and socio-psychological adjustment- in order to find the optimal educational patterns in children with the recurrent tumors. The specific influence of the different types of treatment should be examined also. METHODS: Two groups of children (age 6 - 14 years old) - under radiation (grop A) and under complex treatment (grout B), with different types of malignancy, and their mothers were examined. Group A of14 girls and 16 boys, group B of 8 girls and 12 boys. Neuropsychological method of complex diagnostic of brain functions, interview, test of parental attitude and testing of defense psychological mechanisms (for mothers) were used. RESULTS: There is no correlation between parental estimation of the children's cognitive capacities and parental estimation. The mental retardation is more evident in group B and in children with the recurrent tumors. The patient's psychological well-being is significantly lower in group B and has negative correlation with the anxiety level of mother in both groups. CONCLUSIONS: The mental development and complex psychological well- being in children with the head brain tumors depends on the type of the treatment and treatment experience as well as on parental attitude towards the children's mental disorders, their education and other developmental sources. Psychological diagnostics and psychological help is necessary in both - children with brain tumors and their families.

P.199. PHARMACOKINETICS OF INTRATHECAL LIPOSOMAL CYTARABINE 19 CHILDREN OF DIFFERENT AGE GROUPS

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PURPOSE: Liposomal cytarabine is a slow-release formulation for intrathecal application The recommended dose for adults is 50mg, pharmacokinetic data for children are scarce. Including our published series of four patients we here report on an extended series of 19 children. METHODS: Pharmacokinetic studies of intraventricular liposomal cytarabine were performed prospectively in 19 patients, 4/19 were < 3 years and received 25mg, 8/19 were 4-7 years and received 35mg and 7/19 were > 8 years old and received 50mg liposomal cytarabine. Dexamethasone was used concomitantly to prevent arachnoiditis. CSF and plasma samples were collected

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before administration, 1 hour, 12 hours, 24 hours, 1 week, and 2 weeks post-dosing. CSF samples were analyzed for free and encapsulated cytarabine, plasma samples were analyzed for free cytarabine. RESULTS: Average elimination half-life in children < 3years (25mg) was 56.7h for free cytarabine and 59.3h for encapsulated cytarabine and cytarabine was detectable in ventricular CSF in 3/4 patients two weeks post-dosing. Average elimination half-life in children 4-7 years (35mg) was 40.9h for free cytarabine and 31.5h for encapsulated cytarabine and cytarabine was detectable in ventricular CSF in 5/8 patients two weeks post-dosing. Average elimination half-life in children > 8 years was 43.7h for free cytarabine and 36.4h for encapsulated cytarabine and cytarabine was detectable in ventricular CSF in 5/7 patients two weeks post-dosing. Cytarabine was detectable above the cytotoxic drug level of 0.1 μg/ml in all patients one week post-dosing. Cytarabine concentrations in plasma just above detection level were found in 18 of 159 plasma samples. In general, liposomal cytarabine was well tolerated. CONCLUSION: The administration of 25mg liposomal cytarabine in children less than 3 years of age, 35mg in children 4 to 7 years, and 50mg in older children shows sufficient drug exposure and appears to be safe and well tolerated with concomitant dexamethasone.

P.200*. MARKERS RELATED TO ANGIOGENESIS ON PEDIATRIC BRAIN TUMORS: STUDY OF 120 CASES

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Pediatric brain tumours are the second most common form of childhood malignancy. Malignant gliomas in children are very rare, comprising 5%-10% of childhood intracranial neoplasms. Medulloblastoma and ependymoma represent 10% and 20%. Pilocytic astrocytoma is the most frequent brain tumor in children, Glioblastoma and pilocytic astrocytoma showed similar vascular pattern but turnover of endothelial and tumor cells were lower in pilocytic astrocytoma. Aim of our study was to characterize tumour vasculature and angiogenic profile of pediatric brain tumours investigating some neoangiogenesis related biomarkers as prognostic factors and to giving potential new insight in targeting tumour angiogenesis. Vascular endothelial growth factor (VEGF) promotes angiogenesis. Plasmalemma-vescicle associated protein (PV-1) and Caveolin (Cav-1) are localized in caveole of fenestrated endothelium with a structural role in permeability. Endoglin is a marker of activated endothelial cells within the tumor. Platelet-derived growth factor receptor (PDGFR) is implicated in tumorigenesis and angiogenesis. WT1 is a transcription factor involved on angiogenesis. We performed an immunohistochemical study on 120 pediatric patients, which underwent surgery in our Institute. They were: 45 pilocytic astrocytomas, 12 glioblastomas, 35 ependymomas and 28 medulloblastomas. We analyze the expression of: PV-1, Cav-1, endoglin (CD105), VEGF, PDGFR-α and WT-1. On some cases we confirmed the presence of mRNA of these molecules using Real Time-PCR. Our data were related to clinical outcome. We found PV-1, Cav-1 and endoglin expressed in neoplastic endothelial cells, particularly in proliferating vessels. In glioblastomas we observed expression of PV-1 also in perivascular tumour cells, on the contrary we never found this feature on pilocytic astrocytomas. In ependymomas, Cav-1 was higher expressed on anaplastic tumours. Glioma patients showed a significant different expression of WT1 and PDGFR-α in endothelial and neoplastic cells, related to malignancy grade. VEGF was mainly expressed in glioblastomas. Different expression of WT1 in endothelial and neoplastic cells, related to malignancy grade, was also found in ependymomas. Co-expression of WT1 and VEGF was also detected in ependimoma and medulloblastoma. In our study Caveolin and WT-1 seem to be prognostic factors in ependymomas, while PV-1 and PDGFR-α mainly in gliomas. In conclusion, the different expression profiles of these endothelial markers can help to evaluate the different mechanisms of angiogenesis in pediatric brain tumours, suggesting new prognostic markers and potential therapeutic targets.

P.201*. STUDY OF BIOLOGICAL FACTORS OF SPANISH CHILDHOOD MEDULLOBLASTOMAS, FOR FUTURE THERAPEUTIC STRATIFICATION

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INTRODUCTION: The spanish participation in SIOP collaborative protocols, and consequently, the centralization of biological studies designed for Standard Risk childhood medulloblastoma (MB), in future protocols, made necessary the development of techniques in the reference hospital (Cruces University Hospital). We have studied retrospectively a non-uniformly treated cohort using combined clinical, pathologic and molecula variables. METHODS: Paraffin-embedded (FFPE) tissue samples from 49 pediatric patients submitted from 13 Spanish hospitals were analyzed using fluorescent in situ hybridization (FISH) to study the expression of MYCC and MYCN using Vysis specific probes and immunohistochemistry with a SIOP-E BTG operative protocol, standarized for β-catenin. Detailed clinical data were available for all these patients. RESULTS: Mean age at diagnosis was six years (1-16). Classic MB dominated the study, contributing 58% of all tumors, followed by Nodular/Desmoplastic (ND) MB which contributed 32% of the cohort and finally, Large cell/Anaplastic (LCA) MB (10%). A combination of metastatic disease and LCA phenotype were the clinicopathologic variables associated with poorer overall survival. All MYCC and MYCN amplified tumors, within classic and LCA histological subtypes were metastatic tumors and were associated to poor outcome, except one patient with localized classic MB and MYCN amplification that remains alive. MYCN and MYCC amplification was not found in ND tumors. Survival for this group was 75%, 67% for classic type and less than 20% for LCA tumors. β-catenin nuclear expression only was found in two localized tumors. COMMENTS: High Risk disease has been defined by clinical findings (M+ disease), pathological subtypes (LCA variant) and in recent years molecular markers (MYCC and MYCN amplification). Our results in a cohort of medulloblastomas support this criteria, although we were not able to validate the prognostic role of β-catenin nuclear expression in this study that could be different with the increased number of samples that are entering the study.

P.202. GAMMA-KNIFE RADIOSURGERY IN THE MANAGEMENT OF PEDIATRIC CRANIOPHARYNGIOMA

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INTRODUCTION: Craniopharyngioma is the third most frequent brain tumour in pediatric patients. Histologically a WHO grade II lesion, it displays an epithelial growth pattern in critical, deep neural and endocrinological structures that confers it an aggressive behaviour. Treatment options have been historically debated. Various modalities have been used and, among surgeons, different operative objectives have been proposed. Recent tendency is towards multimodal management. METHODS: We present a series with our experience between 1993 and 2012. We have treated 19 pediatric patients (aged 18 or less), 7 males and 12 females, with a median age of 13 years (range 3-18). Initial symptoms included visual alterations in 15 (78'9%), hormonal abnormalities in 13 (68'4%), headache in 4 (21%) and other symptoms (ataxia hemiparesis, hydrocephalus, seizures) in 5 (26'3%). Seventeen patients (89'4%) had been previously treated with one or more surgeries, 6 (31'6%) with cyst drainage, and 1 (5'2%) with conventional radiotherapy. All patients were treated with a Leksell Gamma-Knife (GK), in a single-session protocol, under general anesthesia (in those younger than 12) or mild sedation. Mean marginal dose was 13'4 Gy (range 9-15), mean maximum dose was 22'1 Gy (18'5-30), mean isodose was 63'5 % (50-75), and the mean number of isocenters was 11 (1-25). Mean follow-up was 51'5 months (8-134). RESULTS: After the aforementioned treatment, 14 patients (73'6%) had a stable clinical course. Of them, 9 (47'3%) did not require other treatments, while 5 (26'3%) underwent additional therapies (surgery in 1 case, intralesional radiotherapy in 1 case, concomitant or subsequent cyst drainage in 3 cases). Three patients (15'7%) suffered progression of the disease, leading to death in 2 (10'5%). Two patients (10'5) were lost to follow-up. CONCLUSIONS: In our experience, surgery followed by Gamma-knife radiosurgery over the neoplastic remnants, with stereotactic drainage of cysts when indicated, and with intralesional chemotherapy in selected cases, is an effective and safe therapeutic algorithm. It offers high tumour control rates without relevant side effects, whether in the optic pathway or in hypophyseal-hypothalamic region. This control rate is achieved in most cases without the need of additional therapies. If needed, additional interventions are not contraindicated before, concomitantly or after GK radiosurgery.

P.203. MULTIMODALITY TREATMENT OF EMBRYONAL TUMORS

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BACKGROUND: Embryonal tumors included medulloblastoma, PNET and AT/RT are the most common form of pediatric malignant brain tumor. Recently, multimodality treatment that combined with surgery, chemotherapy and radiation therapy is performed in embryonal

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tumors. Even though tremendous effort has been made to optimize treatment of patients with embryonal tumor, the prognosis remains poor. PURPOSE: The aim of the present study is to reveal a role of multimodality treatment for embryonal tumors. SUBJECTS: Between April 1984 and December 2011, a total of 43 patients (25 men, 18 women) with a new histological diagnosis of medulloblastoma, PNET and AT/RT classified according to the World Health Organization criteria were included in a retrospective study designed to evaluate the efficacy of surgery, chemotherapy and radiation therapy. The histological diagnosis was medulloblastoma in 31 patients, PNET in 9 patients and AT/RT in 3 patients. After 2004 we have treated with the radiation therapy and intensive conventional chemotherapy with the neuroradiologist and pediatric oncologist to perform safer and more effective therapy. RESULTS: The median age at diagnosis was 5.0 years (range, 0 day -13 years). For the entire study population, the median progression-free survival (PFS) was 24.5 months and the median overall survival (OS) was 41.5 months. 18 of 43 cases were treated with the neuroradiologist and pediatric oncologist and 12 cases (66.7%) survived. Extensive removal prolonged both the PFS ($P = 0.03$) and OS ($P = 0.02$) significantly. In medulloblastoma, no leptomeningeal dissemination in the recurrent cases with cooperation of the neuroradiologist and pediatric oncologist, while in the 9 of 13 cases (69%) treated with the conventional protocol. In the cases with the leptomeningeal dissemination at initial examination of medulloblastoma, had a poor prognosis despite optimal treatment with surgery, adjuvant chemotherapy and radiation therapy. CONCLUSIONS: Multimodality treatment cooperating with the neurosurgery, neuroradiology and pediatric oncology teams may improve the outcome of the patients with embryonal tumors, though further study and a larger randomized clinical trial are required.

MENINGIOMAS

P.204. IMMUNOHISTOCHEMICAL ANALYSIS OF LRIG PROTEINS IN MENINGIOMAS: CORRELATION BETWEEN ESTROGEN RECEPTOR STATUS AND LRIG EXPRESSION

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The leucine-rich repeats and immunoglobulin-like domains (LRIG) protein family is comprised of three integral membrane proteins: LRIG1, LRIG2, and LRIG3. LRIG1 is a negative regulator of growth factor signaling. The expression and subcellular localization of LRIG proteins have prognostic implications in primary brain tumors, such as oligodendrogliomas and astrocytomas. The expression of LRIG proteins has not previously been studied in meningiomas. In this study, the expression of LRIG1, LRIG2, and LRIG3 was analyzed in 409 meningiomas by immunohistochemistry (IHC), and potential associations between LRIG protein expression and tumor grade, gender, progesterone receptor (PR) status, and estrogen receptor (ER) status were investigated. The LRIG proteins were most often expressed in the cytoplasm, though LRIG1 also showed prominent nuclear expression. Cytoplasmic expression of LRIG1 and LRIG2 correlated with histological subtypes of meningiomas ($p = 0.038$ and 0.013, respectively). Nuclear and cytoplasmic expression of LRIG1 ($p = 0.003$ and 0.004, respectively) and cytoplasmic expression of LRIG2 ($p = 0.006$) was correlated with ER status. This study is the first to examine the expression of LRIG proteins in meningiomas, and it shows a correlation between ER status and the expression of LRIG1 and LRIG2, which suggests a possible role for LRIG proteins in meningioma pathogenesis.

P.205. EFFECTS OF BORON NEUTRON CAPTURE THERAPY FOR MALIGNANT MENINGIOMAS

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OBJECTIVE: Malignant meningioma is difficult pathology to control as well as glioblastoma. We tried to control malignant meningiomas by tumor-selective intensive particle radiation, boron neutron capture therapy (BNCT). METHODS: Since June of 2005, we applied BNCT for 19 cases of recurrent malignant meningioma with 27 times neutron irradiation. They were 12 anaplastic, 2 papillary, 1 rhabdoid, 3 atypical meningiomas and 1 sarcoma transformed from meningioma. All cases had been treated with repetitive surgeries and radiotherapies. We applied ^{18}F-BPA-PET before BNCT in 18 out of 19 cases. Here BPA is therapeutic compound boronophenylalanine, itself. One case received methionine-PET instead of it. RESULTS: Seventeen out of 18 cases who received BPA-PET study showed good BPA uptake more than 2.7 of Tumor/Normal brain (T/N) ratio, which indicated more than 2.7 times higher particles were irradiated to tumor cells compared to normal cells and ensured successful treatments. One atypical meningioma case showed 2.0 of T/N ratio. Original tumor sizes were between 4.3 to 109 ml. Mean volume reduction of 64.5 % was obtained after BNCT only within 2 months. Five cases are alive and MST after BNCT was 13.1 (95%CI: 8.6 - 24.6) months. Clinical symptoms before BNCT such as hemiparesis and facial pain were improved after BNCT, in almost all symptomatic cases. A huge atypical meningioma which arisen from falco-tentorial junction and extended bilateral occipital lobes and brain stem, visual problems were worsened after repetitive BNCT with increase of peritumoral edema. Major cause of death was systemic metastasis (5 cases) and CSF dissemination (3 cases). Local tumor progression as a cause of death was observed in 2 cases. In 5 cases, intracranial distant recurrence which was out of BNCT irradiation field was observed during the clinical course. There was no continuity of these distant lesions from original sites. Radiation necrosis was observed in 6 cases but they were controllable except one case. Apparent pseudoprogression was observed at least in 3 cases. CONCLUSION: Malignant meninigiomas are seemed to be good candidate for BNCT.

P.206. CLINICOPATHOLOIGICAL CHARACTERISTICS OF CYSTIC MENINGIOMA

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The meningioma with the cyst is rare, and the differentiation from the malignant brain tumor may be sometimes difficult in images. we analyzed retrospectively our cases of cystic meningiomas and reviewed the literature with regard to imaging features,histopathological results. A retrospective review of 267 patients with intracranial meningiomas that were operated on between April 2001 and April 2011 was undertaken. Of these 20 (7.4%) were associated with cysts. In this series there were 13 male and 7 female patients, mean age was 56.4 years. Tumor location was seven parasaggital, five convexity, three falx, two petrous, two sphenoid ridge, one tubellculum sella. The cysts were classified into intratumoral and peritumoral cysts according to the classification method described by Nauta. There were 14 intratumoral cysts and 6 peritumoral cysts. At operation Simpson grade I resection was eight cases and grede II in nine cases, grade III in two cases and grade IV in one, removal rate was relatively good. (gradeIandII, 85%) Histopathologically, ten were meningothelial (50%) and most transitional, fibrous were observed, but malignant meningiomas were four (20%: three atypical and one anaplastic) and observed in only intratumoral cyst. We suggested that meningioma with intratumoral cyst is more likely to be a malignant meningioma and shoud be completely removed at surgery.

P.207. PLANNED SUBTOTAL RESECTION IN LARGE SKULL BASE MENINGIOMAS FOLLOWED BY GAMMA KNIFE RADIOSURGERY: PRELIMINARY RESULTS

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INTRODUCTION: The management of large meningiomas of the skull-base remains challenging, with microsurgery being the main treatment option. Several series have shown suboptimal cranial nerves outcome and other neurological deficits after complete resection. Planned subtotal resection is now being increasingly considered to reduce the risk of neurological deficits. The residual part of the tumor can then be treated with Gamma Knife Radiosurgery (GKR) to achieve long-term growth control and to maintain optimal neurological functions after planned subtotal resection. METHODS: This case series documents early results following planned subtotal resection followed by GKR (Leksell Gamma Knife Perfexion, Elekta, Sweden), in patients managed between July 2010 and March 2012. There were 8 patients who underwent combined treatment (7 females and one male) for meningiomas. The mean age was 56.37 years (range 33.9-73.3). The mean follow-up period was 10.87 months (range 4.3- 22.1). We analyzed clinical symptoms for all patients, as well as audiograms, ophthalmological and endocrinological tests, when indicated. The clinical outcomes

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and tumor control at latest follow-up are reported. RESULTS: Four patients with clinoid meningioma (mean diameter 26.5 mm; range 17-42) underwent resection of the tumor and the residual component in the cavernous sinus was later treated with GKR. The pre-operative visual status remained stable in 3 patients and one patient had complete visual recovery. There was no endocrine dysfunction following treatment of these tumors. Four patients underwent subtotal resection of petro-clival meningioma (mean diameter 36 mm; range 32-42). Three patients had House-Brackmann (HB) grade 2 facial function, that recovered completely, and one patient continues to have a HB grade 4 facial deficit following surgery. There were no other cranial nerve deficits, or other complication, in this group following treatment. CONCLUSIONS: Our data suggest that planned subtotal resection followed by GKR for skull-base meningiomas has an excellent clinical outcome with respect to preservation of cranial nerve function, with a good possibility of recovery of many of the pre-operative cranial nerve deficits. The results in terms of tumor control needs further long-term evaluation.

P.208. VASCULAR ENDOTHELIAL GROWTH FACTOR SIGNALS THROUGH PLATELET-DERIVED GROWTH FACTOR RECEPTOR β IN MENINGIOMAS IN VITRO

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BACKGROUND: Vascular endothelial growth factor (VEGF)-mediated angiogenesis mediates tumor growth and metastasis. Meningiomas are primarily benign, slow-growing, but highly vascularized tumors. Besides VEGF, there is little data on the function of major angiogenic proteins in meningiomas. METHODS: VEGFA, platelet-derived growth factor-B (PDGFB), their respective receptors_ VEGF receptor 2 (KDR) and PDGF receptor β (PDGFRβ)_ were quantified by real-time PCR and TaqMan® Protein Assay in meningiomas in vivo and in vitro. Human normal brain and dura were used as reference. The effects of VEGFA and PDGFB on primary meningioma cells were examined. As control human umbilical vein endothelial cells (HUVEC) were used. Also the effect of tyrosine kinase inhibitors (Sunitinib and Tandutinib) was determined using gap cell migration assay. Whereas Sunitinib equally inhibits both KDR and PDGFRβ, tandutinib preferentially inhibits PDGFRβ. Furthermore the effect of gambogic acid was analyzed, which inhibits cell migration by suppressing PDGFRβ tyrosine phosphorylation. RESULTS: Most meningiomas displayed no KDR protein expression. PDGFRβ levels were elevated in meningiomas compared with brain ($P < 0.0001$). Also meningiomas displayed inconsistent VEGFA and low PDGFB expression. VEGFA stimulation significantly increased PDGFRβ expression after 24 hours ($P = 0.035$). To confirm VEGFA signaling through PDGFRβ primary meningioma cells were stimulated with 10 ng/ml VEGFA, which induced PDGFRβ tyrosine phosphorylation (fold change $= 3.85 \pm 0.92$) similar to PDGF-BB-stimulated PDGFRβ (fold change $= 3.65 \pm 1.86$). Sunitinib and tandutinib equally suppressed migration of meningioma cells in vitro by 50% on average with 3.8 nM respectively 3.6 nM. Migration was also suppressed by 50% on average with 1.6 nM gambogic acid. CONCLUSION: Collectively, our data suggest that VEGFA primarily regulates VEGF-mediated migration through PDGFRβ, not KDR, in meningiomas. The inhibitory activity of tandutinib and sunitinib against meningioma growth in vitro suggests that selective PDGFRβ inhibitors, in combination with VEGF inhibitors, should be evaluated further as potential therapies for recurrent and malignant meningiomas.

P.209. EXPRESSION OF VASCULAREPITHELIAL GROWTH FACTORS VEGF I / II AND AQUAPORIN4 IN MENINGEOMAS AND THEIR IMPACT OF THE PERITUMORAL BRAIN EDEMA

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OBJECTIVE: Although meningiomas are mostly benign tumors, it is a very unusual tumor because of cytogenetic, biological, and clinical aspects. Meningiomas, like other tumors, induce angiogenesis by a paracrine mechanism involving such molecules as vascularepithelial growth factor. VEGF expression is correlated with vascularity, in general and increase with tumor grade. Aquaporin4 seems to induce the perifokal oedema which in some cases causes a severe neurological deficits. In our study we compare the results of VEGF I/II immunohistochemical results and Aquaporin4 ELISA with the cytogenetic results and the peritumoral brain edema (PTBE). METHODS: Tissue specimens from 77 meningioma patients were obtained after surgery between 2009 and 2010 and prepared for FISH analysis. According to our previous results we used two color FISH for chromosomal alterations of chromosome 1, 9, 14, 18 and 22. Tissue specimens were also immunohistochemical stained, immunoblotting were performed to detect the expression of VEGF I/II and Aquaporin4 were detected by ELISA. The results were compared to the FISH results and the PTBE in the preoperative MRI. RESULTS: There is no significant context between the different typical chromosomal aberrations and the expression of VEGF or Aquaporin4. The VEGF expression increase not with meningioma grade. WHO I meningeomas have significantly less brain PTBE or just a mild PTBE (38/41) than WHO II (10/5) or WHO III (0/2) ($p < 0{,}05$). VEGF I does not correlate with the PTBE, but VEGF II is significantly correlated with the PTBE ($p < 0{,}01$); and this independent of the WHO grading. Aquaporin4 ($n = 36$) does not significant correlate with the PTBE. CONCLUSION: The PTBE appears much more in WHO II and III meningiomas. Interestingly VEGF I does not influence the extent of a PTBE, even Aquaporin4 does not in our series. Only VEGF II has an significant impact of the PTBE. The expression of VEGF I and II and also of Aquaporin4 do not correlate with any chromosomal aberrations in meningiomas and histological grading. Still not all factors which induce a PTBE in meningiomas are clear. In addition to gene and protein expression anatomical conditions should be account for the PTBE in each individual patient.

P.210*. HYPERMETHYLATION OF TIMP3 IS A PREDICTIVE DIAGNOSTIC MARKER IN MENINGIOMAS

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OBJECTIVE: Meningiomas are tumors that arise from the coverings of the brain or the spinal cord. In about 5% of the cases, they turn into malignant forms with aggressive clinical behavior and increased risk of tumor recurrence. Meningiomas are cytogenetically well characterized, with normal karyotype or monosomy of chromosome 22. The tissue inhibitor of metalloproteinase-3 (TIMP-3) maps on the long arm of chromosome 22 in the region 22q12. TIMP-3 has an inhibitory effect on tumor development and growth due to its interaction with matrix metalloproteinases. We investigated the prognostic significance of TIMP-3 gene promoter methylation in correlation to cytogenetic marker of progression in meningioma. METHODS: One hundered twenty-seven meningioma patients were operated by open surgery.Tissue specimens from tumors were obtained after surgery and prepared for FISH analysis. According to our previous results we used two color FISH for chromosomal alterations of chromosome 1p and 22. Additionally, methylation of TIMP3 were analysed with MS-PCR. T-test and Pearson correlation were used for statistical analysis. RESULTS: Forty-six% (57/127) of the investigated tumors were WHO I, 45% (56/127) WHO II and 10% (12/127) WHO III meningiomas. The average age of all patients was 56 years (± 14), 55 years (± 13) of the female patients (87/127) and 57 years (± 17) of the male patients (40/127). We found hypermethylation of TIMP3 in 17% (2/12) of WHO III meningiomas, in 14% (8/56) of WHO II and in 14% (8/57) of WHO I meningiomas. The hypermethylation of TIMP3 correlates well to deletion on 1p ($p < 0{,}05$). In case of recurrent meningiomas (24/127) we found in 16% (4/24) hypermethylation of TIMP3. CONCLUSION: These results demonstrate that TIMP-3 hypermethylation is associated with higher histological grades. Also it is even more correlated to the marker of cytogenetic progression as i.e. deletion of chromosome 1p - as most important genetic aberration in meningiomas - and might therefore serve as a marker of progression in histological inconspicuous meningiomas.

P.211. A COMPARISON OF CONVENTIONAL THREE DIMENSIONAL-CONFORMAL RADIOTHERAPY (3D-CRT), AND VOLUMETRIC MODULATED ARC THERAPY (VMAT) FOR MENINGIOMAS

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BACKGROUND: Meningiomas account for 15-20% of primary adult brain tumours. Neurosurgery is the treatment of choice but radiotherapy (RT) after sub-total resection or at recurrence is an effective adjunct. Although acute toxicity is usually mild, late RT effects may be more damaging, including neurocognitive impairment, visual deficits and hypopituitarism. The goal of RT planning is to spare normal structures (organs at risk, OAR) while delivering a homogeneous dose to the target volume (PTV); for meningiomas this is challenging due to the concave shape of the PTV. Conventional 3D conformal radiotherapy (3D-CRT) using 3 intersecting fixed beams is the standard planning technique but can result in suboptimal plans because of PTV concavity. VMAT (volumetric modulated arc therapy) is a complex RT delivery system that uses continuous variation of

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3 dynamic parameters (speed of gantry rotation, beam shaping and delivery dose-rate) to create highly conformed dose distributions. A planning comparison was undertaken to establish the dosimetric advantage of VMAT (RapidArc, VarianTM) over 3D-CRT. METHODS: 12 consecutive patients (8 females, 4 males) receiving RT for meningioma were studied: 60% following surgical resection, 40% at radiological recurrence. All were planned by 3D-CRT and VMAT to a dose of 50.4Gy in 28 fractions, optimising dose to tumour while sparing OAR and normal brain. Structures were delineated on CT/MRI co-registered images. Analytical Anisotropic Algorithm (AAA 10.0.28) was used to calculate the plans. Comparison parameters included mean dose to PTV and Conformation Number (CN, a measure of how well the high dose region conforms to the PTV while sparing normal tissue). A CN of 1 indicates ideal coverage with no normal tissue exposed to high dose. RESULTS: Median PTV was 111cc (range 56-190). Mean PTV dose for 3D-CRT was 50.7Gy (41.3Gy-54.7Gy) $\pm$4.2 (SD) and for VMAT was 50.6Gy (range 50.3Gy-53.9Gy) $\pm$1.3 (SD). CN for 3D-CRT was 0.446 (range 0.32-0.550) and for VMAT was 0.823 (0.70-0.90). Absolute improvement in CN with VMAT was 0.352 (0.206-0.508) indicating significantly less delivery of high dose to normal brain tissue. Normal brain doses: V45 (% volume of brain receiving >45Gy) 3D-CRT 5.93% (3.3%-14.3%), VMAT 1.41% (0.8%-3.8%). V10: 3D-CRT 38.5% (24.25%-46.86%), VMAT 33.7% (24.7%-55.9%). CONCLUSION: 3D-CRT and VMAT achieved comparable mean doses to PTV. However, VMAT achieved better homogeneity and sparing of normal brain from high doses as indicated by the improved CN. Theoretically this might reduce the risk of late sequelae. The volume of brain receiving doses associated with risk of neurocognitive impairment (>45Gy) was lower with VMAT; this was achieved without excessive low dose coverage (V10 values were comparable). Based on these planning data our centre has adopted VMAT as the technique of choice in treating meningiomas.

P.212. A LARGE LONG TERM RADIOLOGICAL STUDY OF MENINGIOMAS, INCLUDING THE FIRST LONG TERM REPORT OF ANTI-PROGESTERONE THERAPY WITH GESTRINONE

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INTRODUCTION: We present a long term study of patients attending a meningioma clinic including a group treated with gestrinone. METHOD: Data regarding diagnosis, management and radiological or clinical progression was collected and analysed. 93 meningiomas were identified in 89 patients, median age of 64 (35-107); follow up of 45 months (3-226). Meningiomas were grouped according to management: total excision (TE) (n = 31), subtotal excision (SE) (n = 14), radiosurgery (n = 6) and conservative management (CM) (n = 42). 19 patients with 20 meningiomas, prescribed gestrinone, had a median age of 82 (56 -97), and follow up of 86 months (13-191). These were separated into groups: TE and gestrinone (n = 2), SE and Gestrinone (n = 7), radiosurgery and gestrinone (n = 1) and gestrinone only (n = 10). RESULTS: 16.1% of the TE group recurred after a median interval of 27 (3-56) months. 50% of the SE group progressed after 38 (7-137) months. 40% of the CM group progressed after a period of 31 (8-99) months. 16.7% in the radiosurgery group progressed after 57 months. No recurrence was seen in the SE and gestrinone group. Of the SE and gestrinone group, 42.9% progressed after 74 (8-107) months. 30% of the CM and gestrinone group progressed after 38 months (31-57). There was no progression in the radiosurgery and gestrinone group. CONCLUSION: Few patients with progression reported clinical symptoms, suggesting that conservative management may be an alternative for some patients. Due to the small sample size in this study, it is not possible to accurately evaluate the effectiveness of gestrinone in the management of meningioma.

P.213. OLFACTORY GROOVE MENINGIOMAS: A RETROSPECTIVE STUDY ON 48 SURGICAL CASES

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OBJECTIVES: Olfactory groove meningiomas compromise approximately 4-13% of all intracranial meningiomas. Because olfactory groove meningiomas tend to be clinically silent and benign tumors, they may grow very large before becoming symptomatic and being diagnosed. Surgery is the preferred method of treatment and the extent of primary surgery is thought be the critical determinant of long-term cure rates. We report a retrospective study of 48 consecutive patients with olfactory groove meningiomas treated by surgical resection in our single institute. METHODS: Between 1993 and 2012, 48 patients underwent surgical resection for olfactory groove meningioma. A retrospective study was analyzed based on the surgical records, histological records, radiological studies, discharge summaries, and follow-up records. RESULTS: There were 25 male (52.1%) and 23 female (47.9%) patients. The mean age was 51.87 years (range, 33-74 years). Mean maximum diameter was 4.5 cm (range, 1.5-9.5 cm). Tumors were operated through the bifrontal (n = 27) and subfrontal (n = 21) approaches. Gross total removal (Simpson grade I or II) was achieved in 45 patients (93.8%) and subtotal removal (Simpson grade $\geq$ III) in 3 patients (6.2%). Surgical mortality was 4.2% (2 of 48 patients). Four patients (8.3%) showed the evidence of recurrence and underwent surgical resection. The mean follow-up duration was 64.9 months (range, 1-216 months). Preservation of olfactory function was achieved in 26 patients (54.2%). Among the 23 patients with preoperative visual deficit, two patients (8.7%) experienced worsening of preoperative visual acuity. CONCLUSION: The recurrence of olfactory groove meningiomas correlated with the extent of tumor resection. Considering the function outcome, preservation of visual and olfactory function is a notable and important benefit in olfactory groove meningiomas. Based on our surgical experience, the subfrontal approach can provide better olfactory function and bifrontal interhemispheric approach can provide better visual outcome.

P.214. MENINGIOMAS AND THROMBOEMBOLIC EVENTS: RESULTS OF A POST-OPERATIVE SYSTEMATIC SCREENING IN A SERIES OF 275 CASES

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INTRODUCTION: Meningiomas carry a high risk of post-operative thromboembolic phenomena (TEP). We applied a systematic post-operative protocol to a series of patients operated for meningioma in order to have an early diagnosis of TEP and eventually prevent severe complications. In this work, we retrospectively reviewed the results of this post-operative screening protocol in a series of 275 patients. PATIENTS AND METHODS: Two-hundred-seventy-five patients (101 Males, 174 Females, Median Age 62 years, range 26-86) underwent surgery for meningioma removal. Seven percent of patients were affected by spinal meningiomas, 29% had skull base meningiomas and 64% had convexity meningiomas. Tumor histology was as follows: 86%, 13% and 1% of WHO grade I, II, and III, respectively. The post-operative screening protocol included the performance of a pulmonary perfusion scintigram for all 275 patients and ultrasound Doppler examination of the lower limbs (248 patients). If the pulmonary scintigram was unclear or suggestive for pulmonary embolism, the patients underwent a confirmatory pulmonary angio-CT scan. RESULTS: Patients symptomatic for thromboembolism were 4%. Nevertheless, pulmonary scintigram resulted positive for pulmonary embolism in about 33% of the patients. Of these patients, 71% had a confirmed positivity for pulmonary embolism at the angioCT scan. Approximately 6% had an ultrasound Doppler examination of the lower limbs positive for deep venous thrombosis. None of the patients undergoing this protocol died of thromboembolism. Significant risk factors for TEP resulted age >65, pre-operative cardiovascular comorbidity, pre-operative KPS < 80, post-operative KPS < 80, post-operative neurological worsening and post-operative reduced walking ability. CONCLUSIONS: Thromboembolic complications have a high incidence in the post-operative period of patients operated for meningiomas. In our series, at least 21% of the 275 patients had strong evidence for TEP. For this reason, neurosurgeons should strongly and promptly encourage physical and pharmacological preventive measures for thromboembolism.

P.215. CYBERKNIFE TREATMENT FOR LARGE INTRACRANIAL MENINGIOMAS

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INTRODUCTION: Meningioma treatment with Radiosurgery is already common practice, although with the new radiation techniques this therapeutic option is extended to a higher number of patients. This includes those with large lesions or those that for any reason are not candidates for surgery and need fractionation or lower doses in order to minimize the dose received by the healthy surrounding tissues. OBJECT: To analyze the preliminary results of CyberKnife treatment in this group of patients in our five year experience. METHOD: Between October 2006 and February 2012, 31 patients with large intracranial meningiomas have

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been treated with Cyberknife using the skull tracking system. One presented an atypical meningioma. Four patients had previous ventriculoperitoneal shunts for hydrocephalus treatment. In seven cases some type of surgery had been performed (mean number of surgeries: 1. Range: 1-3) and no patient had been previously irradiated. The mean age is 66 years (range: 40-87) and 53% were females. In this group all patients had only one lesion. Patients were treated in three non-consecutive (every other day) sessions. The mean dose was 6.8 Gy per session (20.4 Gy in total) in a range of 6-8 Gy (18-24 Gy in total dose). The mean volume was 37.38 cm^3 (range: 12'4 - 127 cm^3). RESULTS: The mean follow up is 24 months (range: 12-52). Local control was obtained in 94.6% of the cases, of which 50.4% presented a mean reduction in size of 36% in relation to the previous volume (from 5% to the complete lesion disappearance in three cases). In no case a progression has been seen. Four patients experienced clinical improvement, and only in one the motor deficit progressed. No new treatment related symptoms have been observed. More than half of the patients (67%) received steroid treatment during irradiation. CONCLUSIONS: Although the follow-up is still short, the preliminary results in these patients are very positive considering their high age and the large mean lesion volume. It is a simple and comfortable technique with a high efficacy and little morbidity.

P.216. CYSTIC MENINGIOMA: TWO INTERESTING CASES

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INTRODUCTION: Cystic benign meningiomas account for only a small percentage of meningioma overall. They usually have a complex radiographic appearance that may suggest a higher grade meningioma or even another brain tumor type. CASE REPORTS: The first case is that of a 57 year old woman who was found to have an incidental right frontal lesion radiographically consistent with a benign meningioma. A tumor cyst was noted at the 4-year radiographic follow-up. The cyst was larger at 5 years and she had developed simple partial seizures. There was concern that the benign meningioma may have transformed into a higher grade lesion. She underwent resection and pathology revealed a WHO grade 1 meningioma. The second case is that of a 49 year old woman who presented with progressive left sided weakness. Neuroimaging revealed a right frontal parasagittal cystic mass that was radiographically concerning for a high-grade glioma. She underwent resection and pathology revealed a WHO grade 1 meningioma. Symptoms improved in both patients and they both remain free of radiographic tumor progression. Neuroimaging and pathological micrographs of both cases will be presented. DISCUSSION: Cystic benign meningiomas represent only 2-4% of meningiomas. Given that they may have a complex, heterogeneous appearance on neuroimging, they may be difficult to distinguish from higher grade meningiomas or other types of malignant brain tumor. Surgery may be necessary to establish a diagnosis, especially in symptomatic patients.

SPINAL CORD TUMOURS

P.217*. OUTCOME OF PATIENTS WITH PRIMARY SPINAL MYXOPAPILLARY EPENDYMOMA: A RETROSPECTIVE STUDY FROM THE MD ANDERSON CANCER CENTER AND RARE CANCER NETWORK

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PURPOSE: To assess the outcome of patients with primary spinal myxopapillary ependymoma (MPE) treated with surgery with or without radiotherapy (RT) or chemotherapy. MATERIALS AND METHODS: The medical records of 140 MPE patients (63 female; 77 male) treated at the MDACC and 7 institutions from the Rare Cancer Network were retrospectively reviewed. Mean patient's age at diagnosis was 35.9 $\pm$ 15.3 years. The majority ($n = 97$; 69.3%) of tumors were lumbo-sacral/cauda equina. Only two (1.4%) patients presented with a thoracic and cervico-thoracic MPE, respectively. Patients usually complained on low back pain ($n = 124$; 88.6%) and impaired lower extremity sensitivity ($n = 112$; 80.0%). Median tumor size was 20x15mm. Seventy six (54.3%) patients underwent surgery only and 62 (44.3%) were treated with surgery and RT. One patient was treated with RT alone and another underwent surgery followed by chemotherapy. Median administered RT dose was 50.4 Gy. Median FU was 107.9 months. RESULTS: Sixteen patients died, 8 of unrelated cause. The estimated 10 year-overall survival is 88.8% (CI95%: 82.5-95.3). Treatment failure was observed in 47 (33.6%) patients. Local failure, spinal distant relapse and brain failure was observed in 42, 16 and 8 patients, respectively. The estimated 10 year-progression-free survival was 57.4% (CI95%: 47.2-67.6). Age was a major prognostic factor for PFS on univariate analysis: the 10-years PFS for patients ≤ 36 and > 36 years were and 39.6% (CI95%: 26.1-53.5) and 80.6% (CI95%: 69.2-92.0) ($p < 0.001$), respectively. CONCLUSIONS: In this large cohort, treatment failure of MPE occurred in around a third of patients. The observed recurrence pattern of primary spinal MPE was mainly local. Younger patients were significantly more likely to present with tumor recurrence/progression.

P.218*. LIGAND PDGF UPREGULATION IN VESTIBULAR SCHWANNOMA

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Schwannomas are tumors that arise from Schwann cells of the peripheral nerves, usually from the vestibulocochlear nerve. Although they are histologically benign, Vestibular Schwannomas (VS) usually cause hearing loss, tinnitus, facial palsy, and when large enough, brain stem compression which may lead to death. VS are usually sporadic and unilateral, but they also appear associated with the Neurofibromatosis type 2 syndrome (NF2), caused by germ-line mutations of the NF2 gene. NF2 is a tumor suppressor located at 22q12 that encodes a protein termed Merlin or Schwannomin. This gene shows mutations or loss of heterozigosity at 22q in up to 60% and 50% of schwannomas, respectively. Merlin interacts indirectly with Platelet-derived growth factor (PDGF) β receptor, reducing signaling. Pathway by PDGF plays a significant role in angiogenesis and tumor development, so our aim is to investigate a possible aberrant expression of PDGF ligands (PDGFA-D) and receptors (PDGFRA-B) in VS. Thirty-one tumors were studied. Total RNA from frozen samples was extracted with QIAGEN RNeasy Mini Kit (Valencia, CA, USA). Nine non-tumor controls were used. GeneChip® Human Gene 1.0 ST Array from Affymetrix (CA, USA) with 28,132 gene-level probe sets with Ensembl support was selected to perform this study. For data validation, qRT-PCR amplifications were performed with TaqMan Gene Expression Assays products in an ABI PRISM 7900 HT Sequence Detection System (Applied Biosystems). The reactions were carried out using the TaqMan Low Density Arrays (TLDAs, Applied Biosystems). Assays selected were: PDGFA-Hs00964426_m1, PDGFB-Hs00966522_m1, PDGFC-Hs00211916_m1, PDGFD-Hs00228671_m1 and PDGFRA-Hs00998026_m1. Although fold changes vary between microarray and qRT-PCR validation, in all cases the trend of up- and down- regulation was confirmed by both techniques. All ligands (PDGFA, 2.8-fold; PDGFB, 6.5-fold; PDGFC, 2.15-fold; PDGFD, 6.7-fold) were upregulated in VS, while receptor PDGFRA was downregulated (37-fold) and receptor PDGFRB showed no changes. Homodimer-ligands PDGFAA and PDGFCC, exclusive activators of PDGFRα receptor, were less upregulated than ligands PDGFBB and PDGFDD, which activate PDGFRβ receptors. Therefore, contrary to non-tumoral Schwann cells, VS only seems to express PDGFRβ signal pathway, moreover enhanced by upregulation of its ligands PDGFBB and PDGFDD. Our results showed no PDGFRB overexpression, suggesting that ligand inactivation could represent a better therapeutic target than the already tried of blocking PDGFRβ for these neoplasms.

P.219. A REVIEW OF PATIENTS WITH SOLITARY SPINE METASTASIS

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BACKGROUND: Metastases to the spine are a common problem in cancer patients, with reported frequencies of up to 40%. Although spinal lesions are often solitary, there remains uncertainty regarding the factors

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impacting further cancer spread and other patient outcomes. We performed a retrospective review of consecutive patients with solitary spinal metastasis who presented to our institution. The review included a description of the natural history of the disease, treatment modalities, and patient outcomes. METHODS: Records of patients presenting to M.D. Anderson between 1998 and 2008 with a newly diagnosed solitary spine metastasis were retrospectively reviewed. Data on patient demographics, past and present medical history, diagnosis, signs and symptoms, functional status, pain, treatment details, post-treatment events, and outcomes including disease progression and survival were recorded. Standard statistical methods for cohort studies were used. The study was approved by the institutional review board. RESULTS: 266 patients with a previously untreated solitary spine metastasis were reviewed (62% males, median age 64 years). Most tumors were located in the thoracic spine (50%), followed by the lumbar spine (39%). Lung was the most common primary cancer site (27%), followed by prostate (17%), kidney (15%), breast (12%), sarcoma (8%). Eight percent were of unknown primary origin. 54 patients (20%) developed an extraspinal metastasis during follow-up. Of those, the first such metastasis was an extraspinal bone (63%), lung (18%) and visceral (17%) metastasis. The median Kaplan-Meier estimate of time to development of an extraspinal metastasis was 6.5 months (95% confidence interval 4.7-8.3 months). Among individual preoperative characteristics, an extraspinal metastasis developed more frequently in patients with a lung or sarcoma primary (log rank test $p = 0.05$). The median overall survival from the diagnosis of the spine metastasis was 28.3 months (95% confidence interval, 20.3 to 36.3). Preoperative factors associated with survival included primary histology and patient functional status. The impact of management practices will be presented. CONCLUSIONS: Several preoperative factors affect the development of an extraspinal metastasis in patients with an initial solitary spinal metastasis and the overall survival in these patients. These factors are mainly related to the cancer site, as well as the patient's functional status at diagnosis.

P.220. SPINAL MENINGIOMAS: IMMUNOHISTOCHEMICAL EXPRESSION OF MATRIX METALLO-PROTEINASE-9 (MMP-9), HORMONE RECEPTOR STATUS AND SURGICAL CONSIDERATIONS

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Spinal meningiomas (SMs) are rare and show an incidence of 10-15% of all meningiomas and of 20-25% of all spinal tumours. SMs occur more often in women usually between the ages of 40 and 70 years. They arise from mesothelial cell rest found where the arachnoid joins the dura of the nerve root sheaths, creating signs and symptoms of a dermatomal pattern. SMs are frequently located in the thoracic tract followed by cervical, and rarely, lumbo-sacral tracts. Traditional laminectomy for tumour resection may contribute to pain and instability. Consequently we have performed a less invasive surgical approach. In this study, we report a series of 58 spinal meningiomas surgically treated in our Department. In all cases we evaluated the immunohistochemical expression of estrogen (ER) and progesterone receptors (PR). In addition, in order to examine SMs lower biological aggressiveness we analyzed the immunohistochemical expression of MMP-9. The clinical history and the radiological findings were reviewed. All patients were surgical treated by minimally invasive laminectomy preserving arthicularis processes. Ultrasonic cavitation was adopted in many cases for debulking the tumour. Complete excision, including dura and bone (Simpson 1) had been achieved in 10/58 meningiomas (17%); complete excision with reliable coagulation of dural attachments (Simpson 2) had been performed in 37/58 (64%); complete excision of the solid tumour, but with insufficient dural coagulation or bone excision (Simpson 3) had been obtained in 11/58 (19%) of cases. Following histological revision, the SMs were classified as follow: 26 transitional, 8 meningothelial, 8 psammomatous, 7 metaplastic, 5 fibrous, 2 clear cells, 1 angiomatous and 1 atypical. No expression of ER was observed in all cases analyzed, whereby PR immune-expression was found in 86% of cases. A variable MMP-9 expression was evidenced in 73% of meningiomas. A positive significant correlation between MMP-9 and the percentage of PR expression was also observed. As MMP-9 seems to be involved in osteogenesis, we may hypothesize that MMP-9 high expression reflects the acquirement of metaplastic osteogenic properties by the neoplastic cells. With the advent of modern surgical techniques we can perform a less demolitive monolateral laminotomy with possible controlateral vision, without iatrogenic instability, achieving reduced intraoperative bleeding with a general reduction of hospitalization and morbidity. None of our patients underwent fusion.

P.221. 5-AMINOLEVULINIC ACID IS A NOVEL INTRAOPERATIVE MARKER FOR INTRAMEDULLARY SPINAL CORD TUMORS

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OBJECTIVE: Tumor recurrence of intramedullary spinal cord tumors due to incomplete resection is not uncommon. To improve the rate of complete resection of these tumors, an intraoperative marker for visualization of residual tumor tissue is warranted. Currently, 5-aminolevulinic acid (5-ALA) is primarily used for fluorescence-guided resection of intracranial malignant gliomas. However, positive 5-ALA fluorescence was also observed in other intracranial tumor entities. The aim of our present study was to clarify whether 5-ALA might be a reliable intraoperative marker for visualization of intramedullary tumor tissue. METHODS: 5-ALA was administered preoperatively in 12 patients with a neuroradiologically confirmed intramedullary spinal cord tumor. During resection, the tumor tissue was repeatedly examined for potential 5-ALA fluorescence. All tumors were classified according to the current WHO criteria. RESULTS: Positive 5-ALA fluorescence was noted in 7/12 cases, no fluorescence was observed in 5/12 cases: 6/7 ependymomas (5/6 WHO grade II and 1/1 WHO grade III) showed positive 5-ALA fluorescence. Additionally, positive 5-ALA fluorescence was observed in 1 ganglioglioma. The remaining 5/12 cases with no visible 5-ALA fluorescence consisted of 1 diffuse astrocytoma WHO grade II, 1 pilocytic astrocytoma, 1 ependymoma WHO grade II, 1 metastasis and 1 hemangioblastoma. CONCLUSION: According to our results, 5-ALA is a novel intraoperative marker for the visualization of intramedullary spinal cord tumors, in particular ependymomas. The identification of potential residual tumor tissue by positive 5-ALA fluorescence in intramedullary tumors might increase in future the rate of complete tumor resection and thus reduce tumor recurrence.

P.222. SPINAL ROOT HEMANGIOBLASTOMAS IN VHL PATIENTS - FIVE NEW CASES

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INTRODUCTION: Hemangioblastomas are benign tumors, present in the Central Nervous System in at least 75% of patients affected from vonHippel-Lindau (VHL) disease. Their intradural spinal location on the spinal roots is extremely rare. The target of the present paper is to review the clinical and surgical treatment aspects in a series of VHL cases. METHODS: A retrospective review of clinical and surgical reports has been performed on patients treated for spinal root hemangioblastomas within a series of 91 VHL patients, followed and treated in a neurosurgical unit dedicated to Familial Neuro-oncology patients. A review on published spinal root hemangioblastomas has been performed, comparing the results in order to get a common pattern of behavior and management. RESULTS: In our series, a total of five surgical procedures to treat spinal root hemangioblastomas in three patients have been performed. One more case has been diagnosed, but it is being followed and surgical resection has been postponed because it is still asymptomatic. Age of presentation was between 41 and 55 years. The most frequent symptoms were spinal sensitive and motor deficits. The anatomical level was cervical spine in 1 case, lumbar in 2, and sacral in 2 more cases. On neurophysiologic intraoperative tumor dissection monitoring, sensitive but no motor deficits were observed. In fact, in our cases, tumor was related to sensitive root in all (5/5) of hemangioblastomas. In postoperative follow-up, a clinical maintenance level was observed in pre-and postoperative, evaluation following MćCormicks performance scale. Histopathologic evaluation showed in most of cases neurofilament fibers encased within tumor tissue. CONCLUSIONS: Up to now, 31 spinal root hemangioblastomas have been previously published. We describe five additional cases. Tumors grow more frequently on sensitive spinal root fibers, making total resection of hemangioblastomas possible with minimal or no functional deficits in VHL patients. We suggest that surgical treatment on spinal root hemangioblastomas be performed at clinical symptom beginning, in order to get the best treatment results. Surgical resection should be performed under neurophysiologic monitoring, in order to achieve dissection and resection without motor postoperative deficits.

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BRAIN AND LEPTOMENINGEAL METASTASES

P.223*. NEURAXIS IMAGING IN LEPTOMENINGEAL METASTASIS: A RETROSPECTIVE CASE SERIES

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BACKGROUND: Leptomeningeal metastasis (LM) is a central nervous system metastatic complication of cancer that affects the entire neuraxis. OBJECTIVE: Quantify imaging (brain and spine MRI and radio-isotope cerebrospinal fluid [CSF] flow study) abnormalities in a retrospective case series of patients with LM. METHODS: 240 adult patients with LM (125 non-brain solid tumor patients with positive CSF cytology; 40 non-brain solid tumor patients with negative CSF cytology; 50 lymphoma and 40 leukemia patients with positive CSF flow cytometry) underwent prior to treatment brain and entire spine MRI and radio-isotope CSF flow studies (FS). RESULTS: Neuraxis MRI in pathologically defined patients was more often normal in hematologic tumors (80-84%) compared to solid tumors (60%). Similarly, FS was more often normal in hematologic tumors (90-92%) compared to solid tumors (72-75%). However, neuraxis MRI and FS abnormalities (i.e. CSF flow obstruction; nodular subarachnoid or parenchymal disease; hydrocephalus) altered therapy by requiring CSF diversion, site specific radiotherapy, systemic chemotherapy or recommending no further therapy in one third of CSF cytology positive solid tumors and 15% of CSF flow cytometry positive hematologic tumors. CONCLUSIONS: Notwithstanding less frequent imaging abnormalities in hematologic tumors, similar to solid tumors imaging abnormalities frequently result in treatment alteration for patients with LM. Consequently, neuraxis imaging is recommended in both tumor categories in patients being considered for LM-directed and in particular intra-CSF chemotherapy treatment.

P.224*. IMPROVING THE PALLIATIVE CARE OUTCOME FOR PATIENTS WITH BRAIN METASTASIS RECEIVING WHOLE CRANIAL RADIATION: A PILOT, MULTICENTER, PROSPECTIVE, RANDOMIZED, OPEN-LABEL, PHASE III STUDY

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BACKGROUND: The aim of this study is to determine the effect of nerve growth factor (cerebrolysin) on improving the palliative care outcome for patients with brain metastasis receiving whole cranial radiation. METHODS: Ninety-one patients with brain metastasis and impaired minimental test were randomly assigned into two groups. Group I (n = 45, 13 patients with severe impairment and 32 with moderate impairment) received brain radiation with cerebrolysin injection. Group II (n = 46, 19 patients with severe impairment and 27 with moderate impairment) received brain radiation only. After treatment, the test was repeated on both groups and the results were compared. RESULTS: In group I, the scores were shifted after treatment from severe to moderate in nine patients, from severe to mild in two patients and two patients had kept their severely impaired scores. The scores were shifted from moderate to mild in 29 patients, from moderate impairment to normal status in one patient and two patients had kept their moderately impaired scores. In group II, the scores were shifted after treatment from severe to moderate in seven patients and twelve patients had kept their severely impaired scores. The score were shifted from moderate to mild in twelve patients, from moderate impairment to normal status in two patients and thirteen patients had kept their moderately impaired scores. CONCLUSION: Adding nerve growth factor to brain radiotherapy is significantly effective in improving the palliative care outcome of patients with brain metastasis presented by impaired minimental test. ($P, < 0.001$).

P.225. ^{11}C-METHIONINE PET AND RADIOTHERAPY DOSE DISTRIBUTION IN THE DIFFERENTIATION OF RADIONECROSIS AND TUMOUR PROGRESSION AFTER RADIOSURGERY OF BRAIN METASTASES

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INTRODUCTION: After radiosurgery of brain metastases a progressive lesion on T1 Gd enhanced MR imaging cannot distinguish between radionecrosis or tumour progression. Although not conclusive, previous studies suggested higher accuracy of ^{11}C-Methionine PET (MET-PET) to differentiate between these two entities. The aim of this study was to determine whether MET-PET improves this accuracy by analyzing the MET PET activity in relation to the actual radiotherapy dose distribution. High uptake of MET in high dose regions might be specific of tumour activity while low uptake of MET might indicate radionecrosis. METHODS: At our institute radiosurgery is applied to patients with 1-3 brain metastases with a dose of 20 Gy prescribed to the 80% isodose covering the MRI T1 Gd enhanced area. MET-PET was performed if the lesion size was increased at a scheduled 3 month MRI follow-up. We retrospectively evaluated 26 patients for which MET-PET was performed and in whom further follow up showed a radiological confirmation on repeated MRI (n = 21) or by histopathology after surgical resection (n = 5). Radionecrosis was defined as a stable or regressive lesion on MRI or histopathologically proven (n = 10). Tumour progression was defined as a progressive lesion on MRI or histopathologically proven (n = 16). MET-PET scans were registered to the MRI/CT dataset used for radiotherapy planning. Mean MET PET SUV values were calculated in the following volumes: the MRI T1 Gd lesion at the time of recurrence, the brain volume receiving 20 Gy or more (V20), the V12-20 and the volume 1 cm outside V12. SUV values were normalized to an uninvolved brain region (rSUV). Additionally a visual comparison of MET uptake to the dose distribution was performed. RESULTS: With ROC analysis rSUV V20 (the ratio of SUV V20/ SUV uninvolved brain) showed the best discrimination (area under the curve 0.969) followed by rSUV MR Gd lesion (0.931), rSUV V12-20 (0.834) and r SUV volume 1 cm outside V12 (0.769). A cut-off rSUV V20 above 1.1 detected tumour progression with a sensitivity of 94% and a specificity of 90%. In case of tumour progression the highest MET uptake was visualized within V20 (10/16) or both within and outside V20 area (6/16). In case. Visual analysis of radionecrosis showed a below normal brain MET uptake in the V20 area in 7/10 cases. CONCLUSION: MET PET with calculation of the rSUV V20 can be used to differentiate between tumour progression and radionecrosis. Tumour progression is characterized by increased MET uptake within the treatment volume whereas radionecrosis is characterized by a center of low uptake beneath the background in the treated volume.

P.226. LEPTOMENINGEAL METASTASES IN METASTATIC BREAST CANCER. SAFETY AND TOLERABILITY OF COMBINED TREATMENT MODALITY INCLUDING INTRATHECAL THERAPY, SYSTEMIC CHEMOTHERAPY AND RADIOTHERAPY

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Breast cancer is one of the most common sources of metastases to the central nervous system, mainly to the brain, less often leptomeninges. It is not clear whether leptomeningeal infiltration(LM) in form of solid tumor and carcinomatous meningitis are two different forms of LM involvement or carcinomatous meningitis is the result of progression localized LM. Factors predicting for longer survival of patients with LM include breast cancer as a primary tumor, good performance status, short time from diagnosis to treatment initiation. Diagnosis is based on clinical symptoms, neurological examination in combination with magnetic resonance imaging and abnormal cerebrospinal fluid parameters. Positive CSF cytological findings are not required for diagnosis confirmation. At present, there are insufficient data on different therapeutic modalities to determine optimal patient management. In years 2009-2012 in Oncology Center in Bydgoszcz, among 320 patients with MBC 14 were diagnosed with LM. Age of patients ranged from 32 to 65 years, with a mean age of 48 years. Mean time from primary diagnosis to diagnosis of brain metastases was 8 yrs. Localization of neoplastic infiltrates - skull - 9 patients, lumbosacral spine - 2 pts, thoracic spine - 2 pts, multifocal localization - 2 pts. Sites of extracranial metastases were - bones, lungs and liver. Biological markers, such as hormonal receptors and HER2 status were: HER2-positive BC - 4 pts, 'triple negative' BC - 4 pts, luminal-type BC - 1 pts, hormone positive and HER2-non-overexpressed - 5 pts. Diagnosis of LM in all patients was based on MRI findings and neurological examination. Only 3 patients have had positive CSF cytological findings. Patients received combined treatment modality - intrathecal liposomal cytarabine, radiotherapy to the involved area. Systemic therapy was used adequately to the biomarkers and the previous therapies. 11 patients received chemotherapy, used regimens were: lapatinib/capecitabine, liposomal doxorubicin, cispaltine, vinorelbine, Docetaxel. 2 patients received hormonotherapy, 1 patient did not receive systemic therapy. Depocyte was administered 6x qw 2 wks. RTH dose was 20Gy/g. 6 pts have received all planed six inthratecal injections. 8 pts did not complete full treatment plan due to pain at the injection site, post lumbar puncture syndrome or technical difficulties of lumbar puncture. All pts have received radiotherapy. The obtained effect - CR - 1 pts, PR - 2 pts, SD - 5 pts, PD - 4 pts. Survival time - 1-19 months, mean - 10 months. There were no specific adverse events

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related to concomitant usage of intrathecal treatment, chemotherapy and radiotherapy. Combined therapy of leptomenigeal metastases is one of an acceptable toxicity is the treatment and allows reduction of disease symptoms.

P.227*. PROGNOSTIC IMPACT OF FLOW CYTOMETRY QUANTIFICATION OF EPCAM+ CELLS IN THE CEREBROSPINAL FLUID OF PATIENTS WITH LEPTOMENINGEAL CARCINOMATOSIS

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Flow cytometry (FC) immunophenotyping has been recently described as a useful tool for the diagnosis of leptomenigeal carcinomatosis (LC) in patients with epithelial-cell tumors. AIM: to determine the prognostic value of FC quantification of malignant cells in the cerebrospinal fluid (CSF) of patients with LC. Patients: 53 patients (36 women; 17 men), median age 58 (range 39-78) from 10 different Spanish hospitals were diagnosed with LC according to clinical data, CSF cytology and/or magnetic resonance imaging. Tumors were distributed as follows: breast (n = 28), lung (n = 16), gastrointestinal (n = 3), and others (n = 3). In the remaining, 2 neoplasms (breast/gastrointestinal) were simultaneously diagnosed in 2 patients, and the primary tumor location was unknown in 1 patient. The most common histology subtype was adenocarcinoma (48/53 patients, 90.6%). Median Karnofsky performance score (KPS) was 70% (40-100). All patients were eligible for different modalities of therapy: intrathecal, IT (n = 17), systemic chemotherapy, sCh (n = 11), holocraneal radiotherapy, Rt (n = 5), or IT + sCh + /-Rt (n = 21). At the end of the study, 9 patients were alive (median follow-up 33.57 weeks, range 7-70.57). METHODS: 53 CSF samples without macroscopic blood contamination were collected in EDTA tubes with an immunofixative reagent. CSF volume ranged between 0.9 and 5.1 ml. The FC protocol used DRAQ5 for DNA staining, and 2 different monoclonal antibodies against the epithelial cell antigen EpCAM. FC categorized a sample as positive for malignancy when ≥ 10 clustered events with a hyperdiploid DNA content were positive for the 2 mAbs used. Results were expressed as a rate of EpCAM+ cells within the CSF cell compartment, and as a number of EpCAM+ cells/mm^3 of CSF sample. Cox regression analysis was used to determine if the degree of CSF infiltration by EpCAM+ cells had influence on survival. RESULTS: FC detected EpCAM+ cells in 40/53 cases (75.4%). Median rate of EpCAM+ cells was 4% (0-91.9%). Median number/mm^3 was 0.4 (range 0-113). Using a cut-off point of ≤8% EpCAM+ cells (≤0.55 cells/mm^3) *vs* >8%, 2 groups of patients were established. Statistically significant differences on overall survival were seen between patients with ≤8% or >8% EpCAM+ cells (p = 0.014), with an OR = 2,105 (CI 95% (1.164-3.802). Median overall survival was 12.85 *vs* 7.71 weeks for patients with ≤8% and >8% EpCAM+ cells, respectively. This difference was preserved regardless the type of treatment received (IT, sCh or IT + sCh). Regarding age and KPS, no differences were found between groups, but a higher number of males with lung adenocarcinoma were found in the group with ≤8% EpCAM+ cells. CONCLUSIONS: FC measurement of EpCAM+ cells in the CSF of patients with CM at diagnosis is a novel prognostic factor for overall survival in patients under therapy. A cut-off of >8% of EpCAM+ cells identifies a group of patients with a two-fold increased risk of death.

P.228. LEPTOMENINGEAL LYMPHOMA TUMORS

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Primary central nervous system lymphomas and meningeal lymphoma tumors highly differ form nodular lymphomas. There are different kinds of lymphomatous central nervous system involvement - primary central nervous system lymphomas (PCNSL), lymphomatous meningitis with positive CSF cytological findings and leptomeningeal lymphoma in form focal lesions with negative CSF findings, but frequently with bone involvement. PCNSL treatment requires multimodality approach - systemic, intrathecal and radiation therapy. Lymphomatous meningitis therapy consists of inthrathecal usage of cytarabine and methotrexate with liposomal cytarabine being golden standard. Leptomeningeal lymphoma tumors require multidrug chemotherapy regimens, intrathecal therapy and radiotherapy. In Oncology Department of Oncology Center in Bydgoszcz in years 2006-2011, 420 patients with lymphoma were treated - 14 of them have had CNS involvement - 4 with PCNSL (including 1 case of T-cell lymphoma), 3 with lymphomatous meningitis as an early relapse of aggressive lymphoma and 7 with leptomeningeal tumour of meninges (3 pts with DLBCL, 2 pts - FL, 1 pt - PTCL, 1 pt - ATCL). Presented symptoms were - headaches, leg weakness and confusion. Diagnosis of meningeal tumor was based on MRI findings and their lymphomatous nature was confirmed by pathological evaluation of collected tissue. None of patients have had positive CSF cytological findings, no flow cytometry of CSF was performed. Presence of extracranial disease was assessed by FDG-PET. Patients received liposomal cytarabine intrathecally once every 2 weeks in combination with intravenous chemotherapy (4x R-CHOP, 1x R-FC, 1x NHL-BFM-90 regimen, 1x MTX) and radiotherapy. Generally, treatment was well tolerated - 1 patients have had transient visual disorder. Results of treatment are - 1 patients recieved complete remission (CR), 4 pts - partial remission, 1 pt - stable disease, 1 pt - progression during treatment. 2 patients received second-line chemotherapy followed by autologous stem cell transplantation. Of all patients who obtained objective response 4 are still alive, 3 have died - 2 of them due to disease progression, 1 because of pulmonary alveolar proteinosis. Follow-up time ranged from 13 to 30 months. CONCLUSIONS: 1. Leptomeningeal lymphoma tumors are distinct type of lymphoma with its specific symptoms, prognosis and treatment 2. Prognosis and treatment depends on lymphoma type. 3. MRI is standard imaging technique for patients with CNS lymphomas; FDG-PET is proper for assessment of extracranial disease.

P.229. PHASE I DOSE ESCALATION STUDY OF SUNITINIB AND RADIOSURGERY FOR BRAIN METASTASES

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PURPOSE: Sunitinib (SU) has shown anti-tumor effect in brain metastases from some solid tumors. Preclinical data has suggested combined SU and radiation improves tumor control. This phase I dose escalation study of SU and radiosurgery (RS) aims to determine the maximum tolerated dose (MTD) of SU when combined with single fraction RS and evaluate treatment toxicity and tumor responses. METHODS: Eligible patients had 1-3 MRI-confirmed brain metastases that were amenable to RS, a pathological diagnosis of malignancy, life expectancy > 3 months and no contraindications to SU therapy. Dose escalation followed a traditional 3 + 3 cohort design with 2 dose levels: SU 25mg po daily (qd) and SU 37.5mg po qd. Single fraction gamma knife RS with 15, 18 or 21 Gy was delivered on day 7 of SU, depending on the size of the metastases. Patients were followed clinically for toxicity and response. Correlative studies included serial MRI (diffusion, dynamic contrast-enhanced (DCE), spectroscopy), DCE-CT and blood/urine collection. RESULTS: A total of 7 patients (pts) have been enrolled and followed for a median 57 weeks: 4 at 25mg OD and 3 at 37.5mg OD. Tumor histologies included renal (2), lung (2), breast (1), squamous cell cervix (1) and tongue (1). Six of 7 pts completed all 28 days of SU. One patient stopped SU 25mg after 9 days due to acute pericarditis (grade 2), which resolved completely with SU discontinuation and short course of high dose aspirin. There have been no dose limiting toxicities, radionecrosis (radiological or symptomatic) and no grade 3-4 toxicities. Most common toxicities included grade 1-2 hematologic toxicity (85.7%), fatigue (71.4%), gastroesophageal reflux (57.1%), bleeding (28.6%). Analysis of correlative studies is ongoing. CONCLUSIONS: The MTD of SU 37.5mg daily with RS has been well-tolerated in this study. An expansion cohort at this maximum level will allow for further evaluation of the correlative imaging and molecular studies to identify early marker of tumor response.

P.230. COMBINED TREATMENT FOR LARGE CYSTIC BRAIN METASTASIS: RADIOSURGERY AND STEREOTACTIC ASPIRATION

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OBJECTIVE: Large cystic metastatic brain tumors can be treated with surgical resection, radiation therapy and stereotactic radiosurgery. However, single treatment modality is not effective to improve the quality of life for patients harboring these tumors. Stereotactic radiosurgery alone is also dangerous when tumor volume is large. Therefore, in the management of large cystic metastatic brain tumors, multimodality treatment, cyst aspiration and radiosurgery is one option. METHODS: The study population consisted of 44 patients (25 males, 19 females. Mean age, 58 years) with cystic metastatic brain tumors treated from January 2002 to January 2010. Most frequent primary focus was lung cancer (non small cell lung cancer 21, small cell lung cancer 4). The number of lesions was as follows, single in 27, two in 5, three in 2 and over four lesions in 10 patients. 17 patients was

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grouped in RPA(Recursive Partitioning Analysis) class 1, where as 19 and 8 patients were grouped in class 2 and 3. Stereotactic cyst aspiration and Gamma Knife Radiosurgery were performed with a single frame application on the same day or several days after with pre and post operative MR guidance. Prescribed mean dose to the tumor margin was 20 Gy. After treatment, patients were evaluated with MRI every 2 or 3 months. RESULTS: Preoperative tumor volume(mean 32.3cc) decreased about 49% after aspiration(mean 15.9cc). After radiosurgery, 12 (27%) patients demonstrated tumor control, 10 (22.7%) patients showed tumor progression and 22 (50%) patients showed remote new metastasis, during mean follow-up period was 33.6 months. During this periods, 21 patients died, most patients died from primary cancer progression or unrelated illness except one who died from progression of brain lesion. The overall mean survival after these procedure was 39.8 months in RPA class1, 38.9 months in RPA class 2 and 12.1 months in RPA class 3 and these results were statistically significant ($P < 0.01$). There was no procedure related mortality or morbidity at the surgery and GKRS or during follow-up periods. CONCLUSIONS: Cyst aspiration and stereotactic radiosurgery reduced tumor volume, relieving acute symptoms, increasing tumor control rates, decreasing complications and increasing median survival. These results support the usefulness and safety of stereotactic radiosurgery after cyst aspiration. This method is especially effective for the patients whose physical condition is poor for general anesthesia and those with metastatic brain tumors located in eloquent areas.

P.231. INTRATECHAL TRASTUZUMAB IN THE TREATMENT OF NEOPLASTIC MENINGITIS: THREE NEW CASES

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INTRODUCTION: Trastuzumab is a major breakthrough in the treatment of HER2+ breast cancer. AIM: To assess outcome and toxicity of intratechal trastuzumab in the treatment of leptomeningeal carcinomatosis (LC) from HER2+ breast cancer. Patient 1: A 48 years-old female diagnosed in 2009 of metastatic breast cancer HER2neu+. She received only 1 line of systemic chemotherapy until diagnosis of LC in May 2011. She presented with diplopia and instability. Cranial MRI was done and LC was diagnosed. Cytology, biochemical and inmunophenotyping were normal or negative. Weekly 25 mg intraventricular trastuzumab by Ommaya reservoir plus systemic trastuzumab and lapatinib was administrated. Almost complete radiological and complete clinical response was achieved three months later. Then, she started receiving 25 mg intraventricular every three weeks. She developed two transient episodes of ventriculitis immediately after drug administration (first and last cycle). She remains alive 41 weeks after diagnosis and has received 19 doses of IT trastuzumab. Patient 2: A 67 years-old female diagnosed of metastasic breast cancer Her 2 neu +++ in 2006. She received 2 prior chemotherapy treatment lines until March 2010 when was diagnosed of brain metastases and LC because of cranial MRI. Whole brain radiotherapy was administered obtaining a disease stabilization until December 2011 when started new neurological decline. Ommaya reservoir was placed. Cytology was negative and inmunophenotyping was positive. KPS was 60-70. She received 10 doses of 25 mg of trastuzumab, weekly, until neurological decline and terminal performance status. No adverse reaction was documented. Patient 3: A 77 years-old female diagnosed in 2006 of metastatic breast cancer Her 2 neu + ++ . She received 4 lines of systemic chemotherapy previous LC diagnosis in November 2011. Patient presented multifocal spinal cord syndrome, MRI, flow cytometry and biochemical CSF compatible with LC. She started IT trastuzumab, first dose by lumbar puncture and the remaining by Ommaya. She is receiving vinolrebine and systemic trastuzumab. Initial dose was 30 mg and then 50 mg. She has received 20 weekly administrations with no adverse reactions and with improvement of neurological function. She was still alive 20 weeks after diagnosis. RESULTS: 49 administrations of IT trastuzumab were performed in three patients with LC from breast cancer and only in 2/49 (4%) were associated with transient adverse reactions. Remarkably, neurological status was improved with a partial and almost complete radiological response in two of them. Survival was 41, 14 and 22 weeks respectively at the time of closing this study. CONCLUSIONS: IT trastuzumab via Ommaya is a safe alternative in the treatment of LC from HER2+ breast cancer. Further studies are deserved to determine doses and efficacy of this treatment.

P.232*. RADIOSURGERY FOR BRAIN METASTASES: SPECIFIC INDICATIONS FOR GAMMA KNIFE IN LIEU OF LINAC IN A SINGLE CENTER USING BOTH METHODS

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INTRODUCTION: Radiosurgery (RS) is gaining increasing acceptance in the upfront management of brain metastases (BM). It was initially used in so-called radioresistant metastases (melanoma, renal cell, sarcoma) because it allowed delivering higher dose to the tumor. Now, RS is also used for BM of other cancers. The risk of high incidence of new BM questions the need for associated whole-brain radiotherapy (WBRT). Recent evidence suggests that RS alone allows avoiding cognitive impairment related to WBRT, and the latter should be upheld for salvage therapy. Thus the increase use of RS for single and multiple BM raises new technical challenges for treatment delivery and dosimetry. We present our single institution experience focusing on the criteria that led to patients' selection for RS treatment with Gamma Knife (GK) in lieu of Linac. METHODS: Leksell Gamma Knife Perfexion (Elekta, Sweden) was installed in July 2010. Currently, the Swiss federal health care supports the costs of RS for BM with Linac but not with GK. Therefore, in our center, we always consider first the possibility to use Linac for this indication, and only select patients for GK in specific situations. All cases of BM treated with GK were retrospectively reviewed for criteria yielding to GK indication, clinical information, and treatment data. Further work in progress includes a posteriori dosimetry comparison with our Linac planning system (Brainscan V.5.3, Brainlab, Germany). RESULTS: From July 2010 to March 2012, 20 patients had RS for BM with GK (7 patients with single BM, and 13 with multiple BM). During the same period, 31 had Linac-based RS. Primary tumor was melanoma in 9, lung in 7, renal in 2, and gastrointestinal tract in 2 patients. In single BM, the reason for choosing of GK was the anatomical location close to, or in highly functional areas (1 motor cortex, 1 thalamic, 1 ventricular, 1 mesio-temporal, 3 deep cerebellar close to the brainstem), especially since most of these tumors were intended to be treated with high-dose RS (24 Gy at margin) because of their histology (3 melanomas, 1 renal cell). In multiple BM, the reason for choosing GK in relation with the anatomical location of the lesions was either technical (limitations of Linac movements, especially in lower posterior fossa locations) or closeness of multiple lesions to highly functional areas (typically, multiple posterior fossa BM close to the brainstem), precluding optimal dosimetry with Linac. Again, this was made more critical for multiple BM needing high-dose RS (6 melanoma, 2 hypernephroma). CONCLUSION: Radiosurgery for BM may represent some technical challenge in relation with the anatomical location and multiplicity of the lesions. These considerations may be accentuated for so-called radioresistant BM, when higher dose RS in needed. In our experience, Leksell Gamma Knife Perfexion proves to be useful in addressing these challenges for the treatment of BM.

P.233. INITIAL EXPERIENCE WITH USING FRAMELESS IMAGE - GUIDED RADIOSURGERY FOR THE TREATMENT OF BRAIN METASTASES

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BACKGROUND AND OBJECTIVE: Current treatment options for brain metatses include surgical resection, stereotactic radiosurgery, whole brain radiation therapy (WBRT), hypofractionated stereotactic radiotherapy, and more recently chemotherapy agents with some degree of central nervous system activity. Since 2010, Novalis frameless image - guided radiosurgery system is available in Riga East University Hospital and we report our initial results using frameless image- guided radiosurgery for the management of brain metastases. MATERIAL AND METHODS: The records of patients with brain metastases who were treated with image-guided radiosurgery in Riga Eastern University Hospital of one or more lesions between January, 2010 and January, 2012 were retrospectively reviewed. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS). RESULTS: Over a 2- year period, 16 patients harboring 28 lesions were treated in our institution. In the patient sample were represented 5 male and 11 female patients with mean age 59.88 years (min = 45, max= 75, SE = 2,194). The majority (n = 8) of patients had brest cancer metastases. 12 patients demonstrated metachronos development of metastasis, whereas the others revealed synchronous development. 12 of 16 patients were treated in a single fraction, but 4 patients were treated

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using fractioned stereotactic radiotherapy in 3-5 fractions. The maximum target diameter, as determined by T1 - weighted contrast - enhanced magnetic resonance imaging were < 4 cm in all patients. Eight patients (50%) received WBRT (3 Gy in 10 fractions to a total dose of 30 Gy) prior to stereotactic radiosurgery, and were treated with SRS for either lesion progression or new lesions. Other eight patients did not have WBRT during the study period. The treatment isodose volume for each metastasis was calculated using GammaPlan software. The total treatment volume for each patient was the sum of the treatment volumes for all treated metastases. The median total treatment volume was 18,63 cm^3 (range 1,85-47.03 cm^3). Median overall survival time of entire group were 9,7 months (95% Confidence Interval 5,38- 14,01 months). CONCLUSIONS: We present our early data and experience to control of brain metastases using frameless image-guided radiosurgery method. Further studies are needed to match the treatment results with other available modalities to optimize and individualize care of patients with brain metastases.

P.234. GAMMA KNIFE SURGERY FOR BRAIN METASTASES FROM OVARIAN CANCER

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BACKGROUND: Brain metastases from ovarian cancer are rare, but their incidence is increasing. The purpose of this study was to investigate the characteristics of brain metastases from ovarian cancer, and to assess the efficacy of treatment with gamma knife surgery (GKS). METHODS: A retrospective review was performed of patients with brain metastases from ovarian cancer who were treated at the Tokyo Gamma Unit Center from 2006 to 2010. RESULTS: Sixteen patients were identified. Their median age at the time of diagnosis of brain metastases was 56.5 years, the median interval from diagnosis of ovarian cancer to brain metastases was 27.5 months, and the median number of brain metastases was 2. The median Karnofsky Performance Score (KPS) at the time of first GKS was 80. The median survival following diagnosis of brain metastases was 12.5 months, and 6-month and 1-year survival rates were 75% and 50%, respectively. The tumor control rate was 86.4%. The KPS (<80 vs. ≥ 80) and total volume of brain metastases (<10 cm^3 vs. ≥ 10 cm^3) were significantly associated with survival according to a univariate analysis ($p = 0.004$ and $p = 0.02$, respectively). CONCLUSIONS: The results of this study suggest that GKS is an effective remedy and acceptable choice for the control of brain metastases from ovarian cancer.

P.235. TOLERABILITY OF LONG-TERM INTRAVENTRICULAR THERAPY ALTERNATING ETOPOSIDE AND LIPOSOMAL CYTARABINE IN 41 CHILDREN WITH MALIGNANT BRAIN TUMORS

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BACKGROUND: Embryonal brain tumors carry a high risk for leptomeningeal dissemination and tumor cells floating in the CSF are often not amenable to systemic and/or antiangiogenic chemotherapy. Treatment options are limited by the lack of effective drugs for intrathecal therapy of non-hematological malignancies. We report on our experience with an intraventricular therapy consisting of alternating courses of liposomal cytarabine and etoposide. PATIENTS AND METHODS: From 2004 to 2012, 41 patients aged 0.5 to 21 years (median age: 8 years) with various malignant brain tumors received intraventricular etoposide 0.25mg (<1year) - 0.5mg on five consecutive days and liposomal cytarabine at a dose of 25mg (≤ 3 years), 35 mg for children 4-7 years, and 50mg for older patients via an indwelling subcutaneous reservoir. Etoposide and liposomal cytarabine were administered every 2-3 weeks until remission was achieved or for 6 months and every 3 - 6 weeks thereafter as consolidation/maintenance therapy. RESULTS: 463 cycles of etoposide (2.5-104mg (median 15mg) cumulative dose, 1-41 (median 7) 5-day cycles per patient) and 258 administrations of liposomal cytarabine (25-905mg (median 200mg) cumulative dose, 1-19 (median 4) per patient) were given. Immediate toxicities such as transient headaches, nausea, and vomiting occurred with both drugs but persisted longer and were more frequent and intense after liposomal cytarabine (11 *versus* 4). In addition, 9 patients receiving liposomal cytarabine developed visual disturbances and 6 intracranial hypertension requiring lumbar puncture for pressure relief. Since all patients received some sort of concurrent anti-cancer therapy, the efficacy of intrathecal therapy cannot be assessed independently. However, 16/41 patients died of local recurrences and only 1/25 surviving patients developed metastases under intrathecal therapy. CONCLUSION: In conclusion, alternating intraventricular liposomal cytarabine and etoposide is feasible, allows for a more dose tense schedule and may produce responses.

P.236*. A RETROSPECTIVE ANALYSIS OF 777 PATIENTS WITH BRAIN METASTASES: OVERALL SURVIVAL AND PROGNOSTIC FACTORS

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PURPOSE: To evaluate prognostic factors, indexes and overall survival of a series of 777 patients with brain metastases (BM) treated with different schedules including at least Whole Brain Radiation Therapy (WBRT) in single institution: a retrospective analysis. MATERIALS AND METHODS: 777 patients with median age 61.3 at diagnosis were treated with surgery followed by WBRT or with WBRT alone in 16.3% and 83.7%, respectively. Dose of irradiation varied from 30 to 40 Gy in fractions of 2 to 3Gy. Some patients (35.1%) received a radiation boost on operative site or on one or two metastases (from 9 to 17.5 Gy in 2 to 3 Gy per fraction). Diagnosis has been established by contrast CT scan (57.6%), MRI (15.6%) or both (26.8%). BM were sustentorial (52.8%), subtentorial (8.9%) or both (38.3%). Primary tumors were lung (63.6%), breast (12%), gastrointestinal tumor (7.7%), melanoma (5.5%), kidney cancer (3.2%) and other sites (8%). Patients were RPA (Recursive partitioning analysis) I, II and III in 11.3%, 70.2%, and 18.5% respectively, GPA (Graded Prognostic Assessment) 0-1, 1.5-2.5, 3 and 3.5-4 in 39.2%, 40.9%, 10.2% and 9.7% respectively. Survival probabilities were calculated using the Kaplan-Meier method. RESULTS: Median survival times after treatment according to RPA I, II and III were: 20.1, 5.1, 1.3 months, respectively ($p < 0.0001$) and according to GPA 0-1, 1.5-2.5, 3 and 3.5-4: 2.5, 5.6, 8.9 and 19.1 months, respectively ($p < 0.0001$). Median survival time according to Karnofsky Performance Status (KPS) was: 11 months for KPS 90-100, 4.5 for KPS 70-80 and 1.3 for KPS < 70 ($p < 0.0001$). Patients with breast cancer had better survival than those with kidney, lung, melanoma or gastrointestinal tumor: 10.2, 6.6, 4.6, 2.8 and 2.1 months, respectively. Patients with basal like breast cancer had worst survival than those with HER, luminal B and luminal A subtypes: 4.6, 17.1, 16.5 and 14.2 months, respectively ($p = 0.7$). In multivariate analysis, independent prognostic factors for survival were, for gastrointestinal tumor: KPS ($p = 0.0003$), number of extra cranial metastasis (ECM) ($p = 0.007$); for kidney cancer: KPS ($p = 0.03$) and number of BM ($p = 0.04$); for melanoma: KPS ($p = 0.003$) and number of BM ($p = 0.04$); for lung cancer: KPS ($p < 0.0001$), control of primary tumor ($p = 0.02$), presence and number of ECM ($p = 0.001$); and for breast cancer: KPS ($p = 0.0004$), control of primary tumor ($p = 0.03$), presence and number of ECM ($p = 0.02$), number of BM ($p = 0.05$) and triple negative subtype ($p = 0.02$). CONCLUSION: Prognostic factors varied by pathology. Our series confirm the strength of prognostic factors used to GPA score, including biological subtype for breast cancer.

P.237*. ROLE OF SURGERY AND POSTOPERATIVE RADIOTHERAPY FOR 329 PATIENTS RPA I OR II WITH 1 OR 2 BRAIN METASTASES

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PURPOSE: To evaluate the role of surgery and postoperative radiotherapy in the management of brain metastases (BM). A retrospective analysis for overall survival of a series of 329 patients with recursive partitioning analysis (RPA) I or II with 1 to 2 resectable BM treated with different schedules in single institution. METHODS: Patients with median age 61.4 at diagnosis were treated either with surgical resection followed by Whole Brain Radiation Therapy (WBRT) or with WBRT alone in 104 (31.6%) and 225 cases (68.4%) respectively. Dose of irradiation varied from 30 to 40 Gy in fractions of 2 to 3 Gy. Ninety-five patients (91.4%) who underwent surgery and 147 (65.3%) who benefited from WBRT alone received a radiation boost to the metastatic site (from 9 to 17.5 Gy in 2 to 3 Gy per fraction). Diagnosis has been established by contrast CT scan (46%), MRI (17.1%) or both (36.9%). BM were located in the cerebral hemispheres (76.6%), in the cerebellum (16.1%) or in these two sites (7.3%).Primary tumors were lung (62.3%), breast (10%), gastrointestinal (8.2%), melanoma (6.1%), kidney (4.9%) and other sites (8.5%).In the surgical group, patients were RPA I and II in 46 and 58 cases (44.2% and 55.8%), respectively

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and had 1 or 2 BM in 94 and 10 cases (90.4% and 9.6%), respectively. In the group of definitive WBRT, patients were RPA I and II in 17 and 208 cases (7.6% and 92.4%), respectively and had 1 or 2 BM in 133 and 92 cases (59.1% and 40.9%), respectively. RESULTS: Median overall survival was higher in RPA I group compared to RPA II group: 21.3 months (n = 63) and 5.9 months (n = 266), respectively ($p < 0.0001$).There was a significant improvement of overall survival in the surgical group compared to definitive WBRT group: 20.2 months vs 5.4 months ($p < 0.0001$). Whatever the type of primitive tumor, patients RPA I or II with 1 or 2 BM who underwent a radiation boost after WBRT alone compared to those who did not received boost had an improved outcome: 6.3 and 3.8 months, respectively ($p = 0.01$), for the surgical group, there was no difference: 20.6 and 20.1 months, respectively ($p = 0.7$).But, regarding the type of primitive tumor, only patients classified RPA II with breast cancer and treated by WBRT with an additional boost had a significantly improved overall survival compared to those who did not have a boost: 26.6 and 9.1 months, respectively ($p = 0.01$). CONCLUSION: Surgical resection followed by WBRT lead to a better outcome compared to WBRT alone for patients with 1 or 2 BM, and for RPA I or II. An additional metastatic boost improved significantly the overall survival for patients RPA II with breast cancer treated by WBRT.

P.238*. SAFETY OF INTRATHECAL CHEMOTHERAPY: AN ANALYSIS OF 627 PROCEDURES

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INTRODUCTION: Intrathecal (IT) chemotherapy is commonly used for the treatment or prevention of neoplastic meningitis (NM). However, the security of this practice has not been thoroughly assessed. AIM: To analyse all the adverse reactions due to IT chemotherapy in a retrospective cohort of onco-haemotological patients. METHODS: We prospectively registered all the consecutive IT chemotherapy procedures done in Hospital Quiron Madrid from 1 February 2007 until 31 January 2012. All of them were performed by the same investigator. Then we retrospectively reviewed the clinical records searching for any adverse reactions related to the procedures. We classified the adverse reactions in terms of severity (mild or severe) according to the EU Directive, as well as casuality according to Naranjo adverse drug reactions probability scale. In addition, we assessed the relationship between the occurrence of adverse events and several factors, including type of tumor, presence of NM, way of administration (lumbar puncture vs. Ommaya) and type of drug. RESULTS: During the study period, 627 procedures were done in 124 patients (76 men and 48 women; age 52.6 15.6). Seven patients (5,6%) had solid tumours and 117 (94,6.%) had haematological diseases. Twenty-eight patients (22.6%) presented with NM at the time of diagnosis or through the course of the disease, while 96 (77.4%) never developed NM. A total of 520 doses (83%) were administered via lumbar puncture, and 107 (17%) were instilled via Ommaya. Fifty-nine (9.4%) adverse reactions were documented. Among them, 32 (54%) were considered severe, and 30 (51%) were due to the drug itself. The incidence of adverse events was higher when an Ommaya reservoir was used (15/107 administrations via Ommaya vs. 44/520 administrations via lumbar puncture; $p < 0.05$). The presence of NM was associated with a higher incidence of adverse reactions (34 adverse events in patients with NM; p: 0.003). However, the type of tumour did not have any influence on the incidence of adverse events. Proportionally, liposomal cytarabine was related with more adverse reactions (15 adverse events; p:009.), especially when it was administered via lumbar puncture (12 adverse events after instillation via lumbar puncture). CONCLUSIONS: Intratechal chemotherapy is a quite secure procedure. Lumbar puncture is safer than the Ommaya reservoir except when liposomal cytarabine is administered. The presence of NM is associated with a higher incidence of adverse reactions.

P.239. CAVITY RADIOSURGERY AND STEREOTACTIC HYPOFRACTIONATED RADIOTHERAPY AS ADJUVANT THERAPY AFTER RESECTION OF CEREBRAL METASTASES

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OBJECTIVE: Tumor bed stereotactic radiosurgery (SRS) is a relatively recent strategy to delay or to avoid whole brain irradiation (WBRT) and its associated toxicities. This retrospective study evaluates the role of tumor bed SRS and stereotactic hypofractionated radiotherapy (SHRT) as an alternative treatment after initial resection of brain metastases to prevent local recurrence. MATERIALS AND METHODS: Between march 2009 and november 2011, 34 resection cavities in 33 patients with no prior WBRT were treated. Seventeen cases received SRS, 17 cases underwent tumor bed SHRT. The median age was 67 years. Twenty-four patients (72%) had single metastases. At the time of irradiation, extracranial tumor was present in 59% of patients. The median Karnofsky performance score (KPS) was 80 (range 60 to 100), 11% of patients were Recursive Partitioning Analysis (RPA) class I, 58% RPA class II. SRS and SHRT were performed a median of 5.5 weeks after tumor resection. The mean target volumes for SRS and SHRT were 10.1 ml (range 2-15.1ml) and 24.3 ml (range 14.8-44.3 ml), respectively. A median dose of 17 Gy to the 100 % isodose line for the SRS was prescribed to the planning target volume (PTV), defined as tumor bed plus 2 mm (clinical target volume) plus 1 mm. A dose of 4 x 6 Gy (5 cases), 6 x 4 Gy (5 cases) or 10 x 4 Gy (7 cases) to the 100% isodose line for the SHRT was prescribed to the PTV. RESULTS: Local control rate at the resection site was 0.90 at six months for patients treated by SRS (two recurrences) and by SHRT (one recurrence) at a median follow up of 10 months after radiotherapy (range, 1-25 months). All patients with local recurrences also had remote brain metastases. One grade 3 and no grade 4 toxicity were reported after stereotactic treatment. Regional control rate at six months was 0.62. A total of 20 patients (61%) developed new distant brain metastasis during follow up. Two patients presented signs of recurrence due to tumor seeding. The median survival was 15.9 months after treatment (range 1-25 months). There was no sign. difference in local and regional control for patients treated with SRS versus SHRT. Fifteen (45%) patients received salvage WBRT with a median time to salvage WBRT of 12.0 months. Median survival after reg recurrence was 6.4 months, 2.9 months without WBRT, 6.5 months with WBRT (not sign.). CONCLUSIONS: Stereotactic radiotherapy of resection cavities is very well tolerated. Local control 6 months after cavity SRS and SHRT compares favourable to surgery alone and seems to be equal to surgery followed by WBRT in patients with 1-3 brain metastasis. However, a considerable amount of patients progress intracranially and need further treatment.

P.240*. OPEN-LABEL, RANDOMIZED PHASE II, OF CONCURRENT WHOLE BRAIN RADIATION THERAPY (WBRT) AND CAPECITABINE (XELODA®) FOLLOWED BY MAINTENANCE CAPECITABINE COMPARED WITH STANDARD WBRT IN BREAST CANCER PATIENTS WITH NEWLY DIAGNOSED BRAIN METASTASIS: THE XERAD TRIAL

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BACKGROUND: Whole brain radiation therapy (WBRT) is considered as the standard of care for breast cancer patients (pts) with CNS metastasis. The role of chemotherapy in these patients is still not clearly defined. Capecitabine (Xeloda®) alone has shown some efficacy, and the use of capecitabine concurrent with WBRT has been suggested as a radiosensitizer. This trial was design to evaluate the efficacy and safety of capecitabine administered concurrently with WBRT, compared to WBRT. METHODS: In this multicenter, national, phase II study, 130 pts were planned to be randomized in two arms: Arm A: WBRT (3000 cGy in 10 single daily fractions) followed by standard of care (capecitabine and 5-FU analogues not allowed); Arm B: WBRT and concurrent capecitabine (825 mg/m2/twice daily X 14days) followed by capecitabine (1000 mg/m2/ twice daily, days 1-14 every 21 days) as maintenance treatment. The main inclusion criteria were: age over 18, ECOG performance status 0 - 2, histologically confirmed breast cancer, newly diagnosed CNS metastasis non eligible for surgery or radiosurgery, no previous treatment for CNS metastases, and no treatment with capecitabine at time of inclusion. The primary objective was the best objective partial or complete CNS response rate according to RECIST criteria after central review. Secondary criteria included overall survival and safety. RESULTS: The study was terminated earlier due to a slow recruitment rate over a 1 year-period. The ITT population comprised 23 patients: 12 in Arm A and 11 in Arm B. The majority of the patients (78%) presented with invasive ductal carcinomas. Patients in Arm B were slightly more limited: 27% were fully active compared to 46% of the patients in Arm A. The objective CNS response rate was higher in arm B (36%) than in arm A (25%) but the median overall survival was higher in arm A (9.8 months - 95%CI[4.3-17.0]) than in arm B (4.6 months - 95%CI[2.3-8.9]). The most frequently reported AEs were headaches (6 pts in each arm), asthenia (7 pts in arm A, 5 in arm B), nausea (4 pts in arm A, 5 in arm B), scalp radiation reactions (6 pts in arm A, 2 in arm B); vomiting (1 pt in arm A, 6 in arm B) and diarrheas (1 pt in arm A, 3 in arm B). Twelve patients (52%), six in each

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arm, experienced SAEs. The most frequent SAE was "general physical health deterioration" (three patients). Two SAEs were considered related to capecitabine: colitis and pulmonary embolism and led to permanent treatment discontinuation and one SAE in Arm B was considered related to WBRT: depressed level of consciousness. Capecitabine was generally well tolerated, nausea being the most frequent AE leading to dose reduction and three patients had to stop the treatment because of capecitabine-related AEs. CONCLUSIONS: This trial revealed no safety signal for concomitant treatment with WBRT and Capecitabine. Unfortunately, the limited number of patients included in this study impedes any definitive conclusion on efficacy.

P.241. IPILIMUMAB IN PATIENTS WITH MELANOMA BRAIN METASTASES, A SINGLE-CENTER EXPERIENCE IN AN EXPANDED ACCESS PROGRAM

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Patients (pts) diagnosed with melanoma brain metastases (MBM) have a poor prognosis with conventional treatment options (surgery and radiation therapy). Ipilimumab (IPI) is a CTLA-4 blocking monoclonal antibody with established activity in pts with pretreated advanced melanoma. We conducted an observational study on the clinical outcome of pts with a prior history of MBM among advanced melanoma pts treated with IPI (3 mg/kg q3wks x4) in an expanded access program at a single Belgian university hospital center. Pts with SD for 3 months' duration after w12 or a confirmed PR or CR were offered additional courses of therapy (reinduction) at the time of PD. Among the 50 pts who were initiated IPI treatment between April 2010 and May 2011, 16 pts (32%) had been diagnosed with MBM before initiating IPI. Only 1 pt had a solitary MBM, all other pts had $\geq$3 MBM. Baseline characteristics for pts with and without a prior diagnosis of MBM were respectively: 8 male / 8 female vs. 20 male / 14 female, median age 44- vs. 50y, 60 vs. 59% BRAF V600-mutant, 100 vs 92% stage IV-M1c, 31 vs. 9% WHO-PS2, LDH >ULN 68 vs. 56%; CRP >ULN 62 vs. 59%; ALC $< 1000/mm^3$ 19 vs. 32%. All pts were pretreated with dacarbazine; 4 pts had no prior therapy for their asymptomatic MBM before the initiation of IPI, 3 pts had been treated with stereotactic RT (stRT), 7 pts with whole brain radiotherapy (WBRT), and 2 pts with WBRT followed by a stereotactic RT-boost. Induction therapy (4 administrations of ipilimumab) were completed by 7/16 (44%) of pts with MBM vs. 24/34 (71%) pts without MBM; 3/16 (19%) of pts with MBM had IPI-reinduction vs 8/34 (24%) pts without MBM. Immune-mediated adverse events (imAE) were mild/reversible (<20% pts experienced CTCAE gr3 imAE and there were no grade 4/5 irmE). imAE were not significantly different between pts with or without MBM at the exception of radiation necrosis of the brain (RNB). Three patients who were treated with RT for MBM prior to the initiation of IPI developed symptomatic RNB (2x gr3, 1x gr2) that were treated with surgery (1x), and/or corticotherapy (2pt). All pts fully recovered from their RNB related neurological symptoms. The best objective tumor response (BOR by RECIST) outside the CNS in pts with vs. without MBM was 1PR (DCR 6%) vs. 1CR/2PR/4SD (DCR 20%); according to the immune-related response criteria (irRC) the BOR was 3PR (DCR 19%) vs. 1CR/2PR/7SD (DCR 28%). After a median follow-up of 18 months (range 7.5-19.3 mths), 32 pts have died (11/16 [69%] with- vs. 21/36 [58%] without MBM). Six- and 12-mths OS were respectively: 37 vs. 61 % and 37 vs. 48% in pts with- and without MBM respectively. The probability for survival did not differ between pts with- and without MBM (HR.76 [95%CI 0.36-1.59]; p.475 by Log-Rank test). We conclude that in our single-center experience with ipilimumab for pts with advanced melanoma treated in an EAP, the outcome of patients with a prior history of MBM was similar to pts without a prior history of MBM.

P.242*. IMPROVEMENT OF OVERALL SURVIVAL IN PATIENTS WITH BRAIN METASTASIS. AN ANALYSIS OF 2003 AND 2010 COHORT IN A COMMUNITY ONCOLOGY CENTER

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BACKGROUND: Emerging systemic anticancer treatments and focal CNS treatments for brain metastases (radiosurgery or surgical excision) had been shown in clinical trials to improve the survival of patients with metastatic malignancy. The extent of improvement of survival of patients with brain metastasis in community setting remained uncertain. METHODS: Consecutive patients with diagnosis of brain metastasis in the year 2003 ($n = 106$) and the year 2010 ($n = 107$) were retrospectively reviewed. CNS involvement by hematological malignancies were excluded. Univariate and multivariate analyses of prognostic factors were performed. RESULTS: Mean age of the 2003 and the 2010 cohort was 66.3 and 61.2 respectively ($p = 0.004$). For both of the cohorts, lung primary accounts for about 70% of cases. The patient cohort in 2010 more frequently received focal treatment for brain metastases than 2003 cohort - 18.7% vs 5.7%, ($p = 0.003$). Systemic treatments, including chemotherapy, hormonal therapy and targeted therapy, were more frequently given in the 2010 cohort (25.2% vs 4.7%, $p < 0.0001$). Median overall survival of the 2010 cohort was modestly improved by about 1 month compared with the 2003 cohort (92 days vs 63 days, $p = 0.003$). Improvement was mainly achieved in patients with Karnofsky Performance Status (KPS) $\geq$70 that 1-year survival increased from 7.2% to 31.3% ($p = 0.03$). In multivariate analysis, focal CNS treatment ($p = 0.002$), systemic treatment ($p = <0.0001$) and KPS $\geq$70 ($p < 0.0001$) were independent predictors of overall survival. CONCLUSIONS: Contemporary patients with brain metastasis managed in individualized basis with multidisciplinary input resulted in improvement of overall survival, especially in patients with good performance status.

P.243. RARE PRESENTATION OF INTRACRANIAL DURAL METASTASES IN PROSTATE CANCER

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BACKGROUND: Prostate cancer is one of the most leading causes of death in men. Metastatic prostate cancer still remains incurable. Bone and lymph nodes metastases are common in contrast to metastases of the central nervous system and meninges. In particular, metastases of the dura mater are quite rare. The frequence of metastases affecting the dura mater is considered to be rare according to case reports. Here we describe two case reports with dural metastases in prostate cancer. CASE REPORTS: We report two cases of 66y and 68y old male patients suffering from prostate cancer and bone metastases. One patient developed a mild hemiparesis right and aphasia 10 years after diagnosis and several chemotherapies and radiation therapy. The other patient suffered from trigeminal neuralgia. Cranial MRIs revealed intracranial metastases and biopsies showed histopathologically tissue of prostate cancer and dura mater. Both patients died several weeks after diagnosis of dural metastases. DISCUSSION: These cases demonstrate the rare situation of dural invasion of prostate cancer. We assumed that improved cancer treatment and regimens result in increased survival but also increased incidence of metastases. The most cancer types causing dural metastases are carcinomas of the lung and breast, adenocarcinomas and renal cell carcinomas. Metastatic tumors can affect several intracranial sites. Cerebral parenchyma is the most common but leptomeningeal compartements can also be involved. But dural metastases are rare and can grow from epidural space as skullmetastases or from the subdural space by hematogenous spread. Neurological symptoms due to intracranial metastases lead to increases morbidity and mortality and reduced quality of life as well. Unusual sites of metastases as dura mater may become more frequent due to improved overall survival. PATIENTS: Suffering from neurological symptoms of the CNS or cranial neuropathies should be considered having dural metastases. Bone metastases in prostate cancer are common while dural metastases of prostate cancer are quite rare.

P.244. PRE-RADIOSURGICAL WBRT DOES NOT VACCINATE THE BRAIN AGAINST DISTANT RECURRENCES FOLLOWING GAMMA KNIFE RADIOSURGERY FOR BRAIN METASTASES

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Introduction and background. Prophylactic whole brain radiotherapy (WBRT) is commonly recommended as prophylactic treatment against distant recurrences (DR). This treatment probably affects micrometastases implanted in the brain at the time of WBRT, but it does not affect tumor cells that implant in the brain at a later time. We hypothesized that WBRT given before Gamma Knife radiosurgery (GK) would significantly decrease the likelihood to develop DR after GK and that this difference is clinically meaningful only if detectable also after more than one year following WBRT. Material and Methods. All 1366 patients treated with GK in Tilburg between June 1, 2002 and June 30, 2011 were included in the analysis. Of these patients, 180 (14%) had WBRT prior to GK. WBRT was given within six months before GK in 52 patients, between 6 and 12 months in 58 patients and more than one year before GK in 70 patients. Distant recurrences developed in 432 patients (32%). Of these, 17/52 patients (33%) developed when WBRT preceded GK within 6 months, 25/58 patients (31%) when WBRT preceded GK between 6 -12 months and 15/70 patients (21%) when WBRT preceded GK with more than a year. The DR were single in 214 (50%), 2-3 in 103 (24%) and more than 3 in 115 (27%) patients. The survival time was longer among the patients who received pre-GK WBRT, 9 months as compared to 7.3 months, an non-significant

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difference (P = 0.11). RESULTS: Fifty-seven (32%) of the 180 patients who received WBRT before GK developed DR. This should be compared to 375 of the 1186 (32%) patients without pre-GK WBRT who developed DR after GK. There was no statistically significant relation between the time between WBRT and GK and the development of DR (P = 0.16). There was a non-statistically significant trend that patients receiving WBRT developed fewer DR than those who did not receive pre-GK WBRT, in average 2.5 lesions as compared to 2.95 lesions (P = 0.11). CONCLUSIONS: The retrospective design and the fact that we do not now why some patients have received WBRT while some others did not, makes the conclusions a bit shaky. Presumably, the cerebral metastatic lesions were deemed more aggressive in the group that did receive pre-GK WBRT. Therefore, we have drawn two alternative conclusions: It is a possibility that the WBRT treated patient represent a more aggressive growth pattern than the patients who did not receive pre-GK WBRT. If so, this higher risk was neutralized with WBRT. It is also possible that micrometastases developing to DR represent a small group of DR, and that the majority develops from tumor cells migrating into the brain later than the date of WBRT. Both conclusions prove our hypothesis wrong. Pre-GK WBRT does not seem to decrease the number of DR significantly, and should therefore not be used as a standard prophylactic treatment for WBRT but be restricted to patients with a very aggressive cerebral secondary disease.

P.245. TEMOZOLOMIDE-CISPLATIN COMBINATION FOR PATIENTS WITH BRAIN METASTASES FROM MELANOMA

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BACKGROUND: There have not been standards of chemotherapy for treatment for patients with brain metastases. The patients (pts) with brain metastases (BM) from melanoma have poor prognoses. The median survival of patients in this group in historic data (with temozolomide alone, nitrosoureas) did not exceed 4-6 months. The main goal of this trial is to assess the efficacy of new scheme of chemotherapy, combined chemotherapy of temozolomide (TMZ) & cisplatin in pts with BM from melanoma. METHODS: 21 pts were treated with combined chemotherapy of TMZ (150/mg/m2/day orally on days 1-5, every 4 weeks) + cisplatin (20/mg/m2/day intravenous on days 1-5, every 4 weeks). The main aims of this study were objective response (OR) - complete response (CR) + partial response (PR) in the brain and in the extracranial sites (ES), median of survival (mOS), 1-year and 2-year survival. RESULTS: Observations were as follows: in the TMZ + cisplatin treated pts there were 7 OR (33.3%) in 21 pts group in the brain (4 CR and 3 PR), and 7 OR (35,0%) in 20 pts group with extracranial metastases (4 CR and 3 PR). The mOS was 8 months. 1-year survival 33,3% and 2-year survival 19,0% was achieved in TMZ & cisplatin group. CONCLUSIONS: Previous results of our study showed promising high efficacy of TMZ & cisplatin, especially in median of survival, in objective responses in the brain and in the extracranial sites, in 1-year and 2-year survival in comparison with in historic data (TMZ alone or nitrosoureas) in patients with brain metastases from melanoma. Further investigation is to be expected.

P.246. LIPOSOMAL CYTARABINE TREATMENT OF CARCINOMATOUS MENINGITIS IN PATIENTS WITH BREAST CANCER

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BACKGROUND: Median survival from the time of carcinomatous meningitis (CM) diagnosis was 18 weeks and 1-year survival was observed in 16% of patients. Median survival of patients with good and poor performance status was 7 and 3 months, respectively ($p < 0.001$) and median survival of patients treated and not treated systemically was 6 and 2 months, respectively ($p < 0.001$). METHODS: In the period between 2010 and 2012, 14 patients with CM from the Breast Cancer Department of the Cancer Center in Warsaw underwent intrathecal chemotherapy with liposomal cytarabine. The CM diagnosis was based on the presence of cancer cells in the cerebro-spinal fluid obtained by lumbal punction and/or by cerebrospinal MRI. Liposomal cytarabine (DepoCyte) is administered as an intrathecal injection of 50 mg every 2 weeks for 5 cycles and followed by 5 cycles of 50 mg every 4 weeks. RESULTS: Generally, the liposomal cytarabine therapy is well tolerated. No serious adverse events were observed. Intrathecal liposomal cytarabine treatment results in a rapid cancer cell count decrease in the cerebrospinal fluid. However this does not seem to correspond with clinical benefits. The majority of the patients required brain or spinal radiotherapy treatment. CONCLUSIONS: An individual timetable of the treatment scheme should be considered in every case according to the clinical status.The attainment of normal cerebrospinal fluid values can be an indication to apply brain or spinal radiotherapy, followed by the continuation of intrathecal treatment by DepoCyte.

P.247*. MENINGEAL DISSEMINATION OF PRIMARY CNS TUMORS

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Meningeal dissemination of primary central nervous system tumors (MD-PCNST) is a serious complication with devastating effects on quality of life. Diagnosis is dependent upon clinical findings, magnetic resonance imaging, or cerebrospinal fluid analysis. Only a few large single institution series studying sensitivity of these diagnostic procedures are available. A retrospective analysis was performed for patients diagnosed with MD-PCNST referred to a single investigator over an 8-year period (2002 to 2010). We calculated the sensitivity of CSF cytopathology and MRI. Diagnostic delay was calculated as the time from symptom onset to objective diagnosis of MD-PCNST. Twenty-four patients were identified. There were ten patients with astrocytic tumors, four with oligodendroglial tumors, four with ependymal tumors, two with embryonal tumors, two with germ cell tumors, one with a choroid plexus tumor, and one with a mixed neuronal-glial tumor. Twenty-two of these patients had MRI scans and nine of them had CSF analyses at the time of diagnosis. The sensitivity of MRI and CSF analysis was 0.91 and 0.22, respectively. Patients had a mean diagnostic delay of 15 days. Three patients were diagnosed with MD-PCNST prior to the onset of new symptoms. This study represents one of the largest series of patients with MD-PCNST evaluated at a single institution. Contrasting with findings in other neoplasms, MRI provides a much higher sensitivity than CSF cytopathology in our experience. With modern diagnostic modalities, MD-PCNST is readily diagnosed.

NEUROTOXICITY AND NEUROPROTECTION

P.248. ROLE OF ALPHA-LIPOIC ACID IN IMPROVEMENT OF PACLITAXEL / CARBOPLATIN INDUCED NEUROPATHY IN METASTATIC BREAST CANCER:AN EGYPTIAN EXPERIENCE

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BACKGROUND: Paclitaxel is considered one of the most active agent in the treatment of metastatic breast cancer either alone or combined with other agents. Neurotoxicity is frequently encountered and may be a dose limiting toxicity. Alpha-lipoic acid is a neuroprotective drug through its antioxidant and mitochondrial regulatory functions. PURPOSE: The purpose of this study is to compare whether treatment with alpha-lipoic acid versus placebo decreases the severity and frequency of peripheral neuropathy in Metastatic breast cancer patients receiving Paclitaxel/Carboplatin. PATIENTS AND METHODS: This is a randomized, double-blind, placebo-controlled study including 40 metastatic breast cancer patients scheduled to receive Paclitaxel / carboplatin chemotherapy with no prior established clinical neuropathy and were stratified into two groups. Group A (n = 20): Patients (pts) received oral alpha-lipoic acid two times daily for at least 24 weeks. Group B: Patients received oral placebo two times daily for at least 24 weeks. Patients' symptoms of peripheral neuropathy were assessed at baseline and then at weeks 6-8, 12, 24, 36, and 48. RESULTS: In group A receiving paclitaxel/carboplatin/alpha-lipoic acid (n = 20), only 30% of patients (6 pts) developed treatment related neurosensory toxicity, 20% (4 pts) developed Grade I neurosensory toxicity and 10% (2 pts) developed Grade II neurosensory toxicity. In group B receiving paclitaxel/carboplatin/placebo, 70% of patients (14 pts) developed treatment related neurosensory toxicity, 50% (10 pts) developed Grade I neurosensory toxicity, 15% (3 pts) developed Grade II neurosensory toxicity and 5% (1 pt) developed Grade III neurosensory toxicity. The neurosensory toxicity difference between both groups was statistically significant(p value 0.02). Regarding neuromotor toxicity, None of the patients in group A developed treatment related neuromotor toxicity while 1 patient in group B developed Grade I neuromotor toxicity.(p value > 0.05). Regarding hearing toxicity, in both study groups only one patient in group B developed Grade III treatment related hearing toxicity and he went out of protocol due to unacceptable toxicity. (p value > 0.05). There was no statistical significant difference between both study groups as regard objective tumor response. (P > 0.05). In group A among ninteen patients evaluable for response, 57.9% (11 pts) achieved Partial Response (PR), 10.5% (2 pts) showed Stationary Disease (SD) and 31.6% (6 pts) had progressive disease (PD). While in group B (n = 19) evaluable for

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response, 52.6% (10 pts) achieved PR, 10.5% (2 pts) showed SD and 36.8% (7 pts) had PD. CONCLUSION: Adding alpha-lipoic acid to Paclitaxel/carboplatin in metastatic breat cancer resulted in improvement of chemotherapy related neurosensory toxicity without affecting the response to treatment. Further larger studies are warranted to document such finding.

P.249. GLIOBLASTOMA LONG-TERM SURVIVORS: COGNITIVE FUNCTION AND QUALITY OF LIFE

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BACKGROUND: Information on the long-term cognitive outcome following treatment of glioblastoma is virtually lacking due to the dismal prognosis of this malignancy. We report here the cognitive function and quality of life of two glioblastoma patients with survival of over 10 years. CASE REPORT: Case 1: A 55-year-old woman presented with headache and behavioural alteration in January 2000, then sudden onset of decrease of consciousness and left hemiparesis. A CT scan showed a contrast enhancing heterogeneous lesion in the right frontal lobe, with intratumoral hemorrhage and severe peritumoral edema with mass effect. She underwent emergency surgery with a gross total resection and pathologic report was grade IV astrocytoma. She received postoperative radiation (RT) 60 Gy and chemotherapy (CT) with BCNU for 3 cycles. BCNU was stopped due to interstitial pneumonitis, that resolved with corticosteroids and CT withdrawal. She has been relapse free for 12 years, with no cognitive deterioration and normal quality of life. Case 2: A 50 year-old-woman presented with attention deficit and confusion in February 2002, and a MRI showed a left frontal 6 cm cystic lesion, with contrast enhancement. She underwent partial resection. Pathology revealed a grade IV astrocytoma, with oligodendroglial features. She received 60 Gy of RT, achieving a complete response. In 2009 her family noticed memory loss and behaviour alteration. Neuropsychological evaluation revealed cognitive deterioration and MRI showed continued complete response but severe bifrontal leucoencephalopathy. In 2011 the patient needed to be institutionalised because the neurocognitive impairment, without tumour relapse. DISCUSSION: Long-term survival is anecdotal in GBM patients. We report here 2 cases of GBM, each with more than 10 year survival. Molecular analysis showed that both were MGMT methylated and IDH-1 mutated. The second case had oligodendroglial features and 1p19q deletion. Even though both received the same RT dose only one developed severe encephalopathy. Understanding the predisposing factors for this cognitive toxicity is needed.

P.250. LATE-ONSET TRANSIENT NEUROLOGICAL DYSFUNCTION AFTER RADIATIONTHERAPY

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Following radiation therapy, late delayed transient episodes of neurologic symptoms eventually associated with headache and seizures, have been previously described in brain tumours patients. Stroke like migraine attacks after radiation therapy (SMART) syndrome has recently been described as a late transient complication of radiatiotherapy. It involves transient, reversible neurological dysfunction which may include migrainous headache, prolonged hemispheric neurological impairment and sometimes seizure activity associated with typical focal gyral thickening of the affected cortex and gyriform contrast enhancement on MRI. To date, only a few patients have been described. We describe 5 patients presenting with recurrent episodes of transient neurological focal deficits eventually associated with headache and seizures, long time after irradiation for brain tumors, All five patients (age 25-54 years) received a consistent radiation dose (60 Gy) for brain tumor and were in complete remission at the time of the first ictal episode. The first episode occurred after a median interval of 9 years after radiotherapy (range, 1-18 years).The most common symptoms during episodes being: motor deficit (4/5), language alterations (4/5), seizures (3/5), depressed level of consciousness (3/5), sensory loss or disturbance (3/5), headache (2/5) and visual disturbances (2/5). EEG showed epileptic abnormalities or more frequently focal/hemispheric slowing in all patients. MRI demonstrated transient focal cortical enhancing lesions in only two patients; DWI showed water diffusion restriction in only one. All patients improved spontaneously or after the administration of corticosteroids and antiepileptic drugs in a period of 1 to 82 days, and MRI findings were normalized 3 months later. Nevertheless two patients never recovered completely. In all patients but one, the episodes were recurrent, either with constant or changing clinical, electrophysiological and MRI characteristics. After a median follow-up of 1.6 years after the first episode, none of the patients proved to have tumor recurrence. In conclusion SMART syndrome is a rare late complication after radiationtherapy and because of the small number of patients reported with either the SMART syndrome following radiation therapy, presentations will no doubt vary across a spectrum: in our series alteration of state of consciousness and multifocal seizure activity were peculiar and complete recovery was not constant.

P.251. SERUM LEVELS OF VITAMIN E AND NERVE GROWTH FACTOR IN PATIENTS DEVELOPING CHEMOTHERAPY-INDUCED PERIPHERAL NEUROPATHY

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INTRODUCTION: Chemotherapy-induced peripheral neuropathy (CIPN) is a frequent adverse event. The precise mechanisms by which chemotherapy (CT) produces peripheral nerve-fibre damage remain partially unclear. Some controversy exists concerning the neuroprotective role of Vitamin E. On the other hand, preliminary evidence suggests that Nerve Growth Factor (NGF) could be involved in CIPN pathogenesis. Present study aims to investigate which is the relationship between vitamin E and NGF serum levels in a cohort of solid-cancer patients receiving platinum and taxane compounds, and their neurological outcome. MATERIAL AND METHODS: 248 blood samples from 108 patients were analysed. 60% out of patients received oxaliplatin (colorectal cancer); 31% received taxane (breast cancer) and 9% were treated with cisplatin (lung or gastric cancer). All patients were assessed periodically every three months up to 12 months after finishing CT. CIPN was graded according with NCI.CTCv3. Neurological examination was registered according with Total Neuropathy Score. Nerve conduction studies were performed at baseline and after finishing CT. Vitamin E and NGF were determined concurrently with each clinical visit and analysed by ELISA and HPLC techniques, respectively. RESULTS: Age was 57,9 + 11,2 (56,5% female) and 85% (n = 92) out of patients developed CIPN. Symptomatic CIPN (grade 2 and grade 3) developed in half of all patients (50,5%). CIPN was grade 2 in 43,2%, and grade 3 in 7,4%. CIPN remained symptomatic in 37% and 23,5% of patients at 6 and 12 months after CT, respectively. In all series, mean serum levels of vitamin E were: 14,8 $\pm$ 3,2 mg/L at baseline; 15,4 $\pm$ 4,2 mg/L mid-treatment; 15,6 $\pm$3,3 mg/L at finishing CT; 15,2 $\pm$ 3,3 mg/L three months after CT; 15,1 $\pm$ 3,2 mg/L six months after and 16,1 $\pm$ 1,8 mg/L at twelve months. At baseline, no differences in serum levels of neither Vitamin E nor NGF were detected between patients that developed or not neuropathy. No differences in vitamin E were obtained at each point of evaluation when comparing both groups. At finishing CT, the variation of NGF when compared with baseline data was 1,17 $\pm$ 1,2 pg/mL in the group without CIPN or grade 1, and 3,3 $\pm$ 4,7 pg/mL in symptomatic (2 and 3) CIPN patients, being differences significant ($p = 0.044$). Moreover, NGF variation showed a positive correlation with patients developing CIPN according if it was symptomatic or not ($r = 0.3$, $p = 0.04$). CONCLUSION: Serum levels of vitamin E do not show a significant variation during and after CT in patients treated with oxaliplatin, cisplatin and taxane drugs. Conversely, a greater increment of serum levels of NGF was disclosed in those patients suffering from symptomatic CIPN when finishing the CT schedule. This increase could be related with the biological response of denervated target tissue as a compensatory mechanism to the neurotoxic damage.

PARANEOPLASTIC NEUROLOGICAL SYNDROMES

P.252*. USE OF BODY-CT AND PET-CT IN THE INVESTIGATION OF PARANEOPLASTIC NEUROLOGICAL SYNDROMES: RETROSPECTIVE AUDIT OF PRACTICE IN A REGIONAL NEUROSCIENCE UNIT IN THE UK

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BACKGROUND: Paraneoplastic neurological syndromes (PNS) are characterised by progressive neurological dysfunction resulting from non-

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metastatic effects of cancer. Positron emission tomography (PET) has emerged as an effective tool for diagnosis and staging of malignancy. An advantage of PET over conventional imaging modalities such as body-CT includes demonstration of metabolically active disease in anatomically normal appearing structures. AIMS: To analyse and improve use of whole-body CT and PET-CT in the investigation of PNS in a regional neuroscience unit. METHODS: Retrospective review of 42 patients with suspected PNS referred for imaging between April 2007-March 2008 was conducted. The data was presented locally followed by recommendations that a consultant neurologist with interest in PNS reviews each case before referral and PET-CT is considered in cases where body-CT is negative. We re-audited 44 patients referred between July 2008-June 2009 and identified each patient's final diagnosis along with any additional investigations undertaken. RESULT: In the first cycle, 42 patients underwent whole-body CT for investigation of PNS. 4 scans were positive for malignancy and 38 were negative, of which only one was followed up with PET-CT. In the second cycle, whole-body CT was performed in 44 patients, of which 11 subsequently proceeded to PET-CT. 5/44 patients had a final diagnosis of PNS, of which only 3 had undergone PET-CT. CONCLUSION: Early PET scanning in clinically suspected PNS may prevent expensive, extensive and often unnecessary investigations. Trust guidelines now advise use of PET-CT rather than conventional body-CT in clinically suspected PNS. We aim to re-audit our practice in due course.

P.253*. A VIEW OF POLYNEUROPATHY AS A PREDICTOR OF POSSIBLE NEOPLASTIC PROCESS

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BACKGROUD: Due to recent studies from 7,5% till 48 % of cancer patients have paraneoplastic polyneuropathy that often becomes clinically apparent long before neoplasm is diagnosed or metastases are verified. AIMS: to reveal possible correlation between the development of polyneuropathy and the existence of neoplastic process that wasn't diagnosed before. METHODS: In Angioneurology Department of V.K. Gusak Institute of Urgent and Recovery Surgery there were 52 patients observed, divided into two groups. The first group consisted of 30 patients with verified diagnoses of neoplastic disease (lung cancer, breast cancer, urinary bladder cancer, stomach cancer, ovarian carcinoma, blood disease). The 2nd group consisted of 22 patients having polyneuropathy detected for the first time. All the observed patients were thoroughly examined neurologically. The severity of polyneuropathy was estimated on the Dyck P.J. (1988) scale and NSS (Neuropathy Symptom Score). Additional methods of examination comprised general clinical tests and oncomarkers analysis (Ca-125, HCG, PSA, Ca 15-3, Ca 19-9, CEA, beta-2-microglobulin). The base method was EMG conducted using 4-channel electromyograph "Reporter" (Biomedica, Italy). RESULTS: 47% of patients with active neoplastic process had EMG-markers of polyneuropathy, such as lowering amplitude of M-answer by 2-2,5 times and reducing of nerve conduction velocity (NCV) to 22-30 m/s. In the second group after oncomarkers analysis and detailed clinical examination neoplastic disease in early stage was revealed at 7 patients (31%). CONCLUSIONS: Polyneuropathy often accompanies active neoplastic process. The existence of polyneuritic clinical picture and the reduction of nerve conductance velocity according to EMG require detailed somatic examination of a patient, which in a number of cases permits to reveal neoplastic process in good time.

P.254*. PARANEOPLASTIC VERSUS DYSIMMUNE DISORDER IN A COHORT OF 87 ANTI-NMDAR ANTIBODIES ENCEPHALITIS, SUBGROUPS ANALYSIS OF CLINICAL SPECIFICITIES AND TUMOURS

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INTRODUCTION: Limbic encephalitis associated with anti-NMDAr antibodies (N-methyl-D-aspartate receptor) has been firstly described in 2007. The typical clinical pattern in young women, with psychiatric symptoms, seizures, memory loss and dysautonomia, is frequently associated with tumour, especially mature ovarian teratoma. Thus, the disorder is of paraneoplastic origin. An atypical clinical pattern and the absence of a tumour are elements encountered with children and male patients. Much infrequent within these subpopulations, this study aims to analyse clinical specificities and triggers of this dysimmune disorder in children and male patients. METHOD: Eighty seven patients have been diagnosed by the Centre de Référence des Syndromes Neurologiques Paraneoplasiques, in Lyon, France, since 2008. Fifty nine patients are adults (48 women - mean age of 28, range between 18 and 66; 11 men - mean age of 24, range between 18 and 66 years old). Twenty eight patients are children and adolescents (21 female - mean age of 12, range between 2 months and 17 years old). RESULTS: Tumour has been found in 19 patients. All are adult women and in 17 cases, a mature ovarian teratoma has been diagnosed. The others type of tumour hare a canalar breast cancer and an ovarian fibroma associated with an uterine leiomyoma. Few patients exhibit prodromal symptoms, like flu-like disease, headache, gastrointestinal symptoms (29/43 adults and 10/20 children): there is no difference between group with or without tumour. Within the 17 mature ovarian teratomas, 2 patients showed a favourable clinical evolution immediately after surgery. All patients have been treated with immunomodulatory drugs and outcome is favourable in a majority of patients, but cognitive sequellae of various severities are present. CONCLUSION: Women with anti-NMDAr antibodies encephalitis arbour a high tendency to have tumours, in most cases these are mature ovarian teratomas: these seem to be a trigger in about 49% of our female cases. Surgery, in our study, leads to an immediate favourable clinical outcome in a minority of patients. Neither male nor children exhibit tumour, even after a long follow-up. The disorder seems to be more dysimmune rather than paraneoplastic within these subgroups. More studies are needed to better understand the genesis of NMDAr antibodies in patients without tumours.

SUPPORTIVE AND PALLIATIVE CARE

P.255. SEIZURES IN HIGH-GRADE GLIOMA PATIENTS: UNDERESTIMATED IN THE END OF LIFE PHASE

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OBJECTIVES: to analyse the prevalence of seizures and use of anti-epileptic drugs (AEDs) in the end of life (EOL) phase of high-grade glioma (HGG) patients and to identify patient characteristics associated with the occurrence of seizures in the last week of life. METHODS: patients were recruited from a cohort of adult HGG patients diagnosed in 2005 and 2006 in three tertiary referral centres for brain tumour patients. Physicians involved in the EOL care for deceased HGG patients were asked to fill in a questionnaire regarding seizures and anti-epileptic treatment both in the last three months and in the last week of life. Data on seizures and use of AEDs before the EOL phase were obtained from medical correspondence and hospital medical charts. RESULTS: out of 155 deceased patients, data of 92 patients were eligible for analysis. Twenty-nine percent of these 92 patients had seizures during the last week of life; 33% of the patients with and 22% of the patients without a history of seizures. Besides a history of status epilepticus ($p = 0.047$), we identified no other significant risk factors to develop seizures in the last week of life. Fifty-eight percent of all patients used AEDs in the last three months of life. In 35% of patients of whom AEDs were tapered, seizures occurred in the last week of life. CONCLUSIONS: our results demonstrate that seizures are a common symptom in HGG patients during the last week of life and emphasize the importance of adequate AED treatment throughout the EOL phase.

P.256. SEIZURE, ANXIETY AND MIDAZOLAM IN THE END OF LIFE OF GLIOBASTOMA PATIENTS

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CONTEXT: The tumour progression remains inevitable and pulls into death almost all patients. The accessible data in the literature about symptomatic treatments in the end of life of gliobastoma patients is very rare. In order to treat better anxiety and epilepsy, the neurooncologists of our university hospital (Nancy-France) usually prescribe midazolam. Otherwise, this molecule does not possess the label Marketing authorization in France in these two indications. Nevertheless, the French Agency of Health and

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Sanitary Safety (AFSSAPS) and the French Society of Support and Palliative care (SFAP) have established recommendations. OBJECTIVE: The main objective of this work is to describe the clinical evolution of seizure and anxiety in end of life of glioblastoma patients treated by midazolam. PATIENTS AND METHOD: We analyzed 65 glioblastoma patient's file who died during year 2011 at the teaching hospital of Nancy. Among these patients, 16 were treated by midazolam during their 28 last days of living. Midazolam prescriptions were analyzed and clinical evolution of anxiety and seizure was evaluated. RESULTS: The main initial symptoms experienced by patients were seizure (69%), anxiety (56%) and paresis (56%). Midazolam has been used by subcutaneous way at a posology waving from 0,2 to 2 milligrams per hour. Eleven patients had seizure and nine suffered from anxiety. Among 11 patients who had seizure, seven had no more after administration of midazolam, Regarding anxiety (even though clinical evaluation is subjective) nine patients were severely anxious, and four remain so after administration of midazolam. Anxiety data of the three left patients is missing. DISCUSSION: Midazolam was administered by subcutaneous way to the all patients, as recommended by AFSSAPS and SFAP. According to AFSSAPS and SFAP, doses should be adapted depending on weight, undernutrition state, the therapeutic effect, medication and seriousness of clinical state. AFSSAPS and SFAP recommend, in anxiety care, to realize a bolus of 0,05 milligram per kilogram (to be renewed once or twice as for AFSSAPS), before establishing a perfusion at a rate of 0,5 milligram per hour. In our study, no patient had bolus but only drips going from 0,2 to 2 milligram per hour over 24 hours. Regarding the symptomatic treatment of seizure, AFSSAPS recommends midazolam use but no doses are defined. Use of midazolam to treat seizure and anxiety by neurooncologists seems to improve patients. Furthermore, its short half-life, its speed of action and the absence of major side effects make the use easy. CONCLUSION - PERSPECTIVES: According to our results and the feeling of the local actors, midazolam seems to be effective in the symptomatic treatment of seizure and anxiety. We still need to better define the indications and dosage rules of use through the implementation of a dedicated database and the establishement of a real prospective trial.

P.257. IS THE CLINICAL NURSE SPECIALIST IDEALLY SITUATED AS THE PATIENTS KEY WORKER TO BREAK BAD NEWS

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The breaking of significant news is a complex issue. As a result of a patient satisfaction survey carried out to be compliant with NICE Improving Outcomes Guidance (IOG) for people with brain and other CNS tumours, patients and their careers identified that although satisfied with the service, many felt that 'breaking bad news' or giving of histology could be improved. The clinical nurse specialist team looked at ways of improving this service to patients and their carers. As a result they implemented a nurse led results clinic, which runs on a weekly basis. meaning that all patients are seen within the time frame outlined in the IOG. Dedicated time was set aside in a Macmillan funded information centre, in an environment away from the main hospital site. DISCUSSION/METHODS: Patient's who have attended the clinic have been sent a questionnaire to assess the clinics success. It poses the question; 'Is the clinical nurse specialist ideally situated as the patients key worker to break bad news' results of a prospective questionnaire based study. RESULTS: 15 questionnaires have been sent out with a response rate of 46%. Of the returned questionnaires, 85% (6/7) felt that the clinical nurse specialist was ideally suited to deliver results, the other 15% (1/7) would have preferred a consultant in charge of their care. When asked if enough information was given regarding further treatment 57% (4/7) stated all treatment options were fully explained with a further 28% stating they received as much information as they wanted. In terms of location, 42% (3/7) felt that the information centre was exactly the right environment for the clinic and a further 28% (2/7) were happy with location. 15% (1/7) felt that the Macmillan branding and information in the centre made them feel uncomfortable, however they remained satisfied with the consultation. Following a 30 minute consultation, patients are given literature to take away with them, including a Macmillan information booklet, information prescription and contact details for their key worker this happened with 85% (6/7) of patients who completed the questionnaire. Conclusion. This small sample of patients are satisfied with their nurse led results clinic, and feel that the Macmillan information centre is an ideally situated location. The questionnaires continue to be sent out to gain further quantitative data to strength and expand the conclusions made in this study.

P.258. ANALYSIS OF SIGNS AND SYMPTOMS, AND TREATMENT OF PATIENTS WITH MALIGNANT GLIOMA IN THE LAST WEEK BEFORE DEATH

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INTRODUCTION: Glioblastoma multiforme (GBM) is the most frequent malignant primary brain-tumor in the adult. Although knowledge about malignant gliomas is expanding, prognosis is still poor with a median survival of approximately one year. As a consequence, there is a high need of a specialized palliative care to keep the quality of life as high as possible. In the end of life period, malignant brain-tumors patients differ, with respect to symptoms and needs, from patients with other oncological diseases. There are no evidence-based guidelines for palliative and supportive care in the end of life phase in malignant brain-tumor patients. The purpose of the study was to prospectively asses signs, symptoms and therapeutic strategies of patients with malignant gliomas in the last week before death in order to improve end of life care in the terminal phase of the disease. METHODS: According to a standardized protocol, data from 28 consecutive patients died due to a malignant glioma in a hospital setting were prospectively analysed. We surveyed demographic data, symptoms, complications, therapeutic strategies, medication and support of the carer in the last week of life. RESULTS: Most frequent neurological signs were hemiparesis, immobility, dysphagia, aphasia and seizures. In Thirty-nine percent of patients pneumonia was diagnosed, a quarter suffered from urinary tract infection. Most frequently administered medication were opioids, heparin, prophylaxis of gastric ulcers, NSAR and anticonvulsive therapy. In more than half of cases, relatives received psychological support by the stuff. DISCUSSION: Results concerning medication, signs and symptoms match with available data in the literature. Due to the fact that all patients suffered from decrease of vigilance and cognitive impairment, specific symptoms as pain are diffuse and difficult to evaluate. Our study shows that there is a need of a specialized supportive care in the end of life phase of brain-tumor patients. Further research is necessary to provide evidence-based terminal care for patients suffering. from malignant glioma. Support services for the patient's family and carers should be. developed.

P.259. EXPLAINING COGNITIVE PROBLEMS DUE TO A BRAIN TUMOR (BT)

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BT patients have brain damage and consequent disturbances in brain function. The spectrum of these disturbances depend on the type and location of the tumor as well as the extent of the diffuse injuries related to the tumor and treatments. Worrisome is that the patient's cognitive symptoms are often underestimated or ignored, especially when the patient's intelligence appears to be well-preserved at the doctoŕs appointment giving a false impression of a well-functioning patient. The neuropsychological examination of these patients is also often disregarded. Higher cerebral functions i.e. mental functions can be divided for clinical purposes into three functional units based on AR Luria: 1) The unit regulating cortical tone i.e. the vigilance upholding system, 2) The unit for collecting, processing and storing information and 3) The complex unit of the frontal lobe and itś connections of the executive functions programming, monitoring and verifying mental activities. This three tiered functional system can be explained to the patients. Illuminated with practical examples from daily life and presented in graph format helps patients and family members understand brain function. Many seem instantly to grasp some implications as to their own problems. On the basis of this functional division many seemingly enigmatic situations can be understood. A very common situation with BT patients is that executive problems and damaged vigilance control make daily life very hard, especially without outside help. Yet, at the doctor's office everything may seem quite normal. This seeming discrepancy in brain damage patients has been noted already more than 100 years ago. BT patients fall into this group often and many have their executive and vigilance problems overlooked or ignored. This is often due to insufficient understanding of brain function by the health care professionals. If, however, this three tiered system is understood, it helps both the professional and the patient to evaluate roughly the scope of the problems. For example: a patient with a frontal glioma instantly pointed at the graph after hearing the explanation. She concluded that her problems were mainly in the executive domain and vigilance problems with related hypersomnia. This was a quite accurate assessment of her

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situation. A frontal meningioma patient with superior intelligence but suffering from executive dysfunction and tiredness noted that he had performed very well in tests of intelligence and information processing, yet could point out where his problems were mostly located when hearing the explanation.Giving this framework at the appointment, added with some practical examples and anatomical pictures, often helps the BT patient and family members to better understand the nature of the symptoms and possibly to better cope with them.

PRIMARY CENTRAL NERVOUS SYSTEM IYMPHOMA (PCNSL)

P.260*. MICRORNAS IN CEREBROSPINAL FLUID AS BIOMARKER FOR DISEASE COURSE MONITORING IN PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA

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The diagnosis of primary central nervous system lymphoma (PCNSL) depends on histopathology of brain biopsies, because disease markers in the cerebrospinal fluid (CSF) with sufficient diagnostic accuracy are not available yet. In our previous study, combined expression analyses of *miR-21*, *miR-19b*, and *miR-92a* in CSF revealed that CSF levels of miRNA could differentiate, with high specificity (96.7%) and sensitivity (95.7%), patients with PCNSL from other neurologic disorders. In the current study, we analyzed miRNA levels in the CSF of individual PCNSL patients (n = 9) at different time points following diagnosis questioning whether miRNAs could potentially serve as markers of disease course. Longitudinal REL data of each indicative miRNA in the CSF of all nine patients correlated well with the clinical courses. Five PCNSL patients who achieved a persistent complete remission showed a marked decrease in miRNA expression levels and turned from positive to negative miRNA status in the CSF. In two patients transient responses to chemotherapy followed by progressive PCNSL were demonstrated in consecutive MRIs. In accordance, the CSF miRNA levels initially decreased and subsequently increased during disease progression as determined by qRT-PCR Finally, markedly increasing levels of CSF miR-21, miR-19b, and miR-92a were observed in one patient with primary progressive disease and in another patient relapsing after a complete remission lasting for 12 months. Interestingly, the CSF miRNA levels correlated to the tumor volume as measured with MRI. This data supports the diagnostic value of CSF miRNA levels for disease course monitoring. Importantly, in contrast to CSF miRNA standard CSF parameters such as total cell count and protein concentration did not show consistent changes correlating with the PCNSL status during treatment and follow-up. A crucial feature of an ideal PCNSL biomarker is that its differential expression indicates the course of disease and provides insight into disease status with greater sensitivity than other diagnostic methods. In our pilot study, serial miRNA measurements agreed with tumor status based on objective criteria in each of nine PCNSL patients. Measurements of individual CSF miRNA expression profiles within prospective clinical studies including larger patient sample may ultimately facilitate early, noninvasive diagnosis, risk stratification, and determination of appropriate therapeutic interventions in patients with indeterminate findings in neuroimaging.

P.261*. PRIMARY CNS LYMPHOMA TREATED WITH HIGH-DOSE METHOTREXATE AND RITUXIMAB - SINGLE INSTITUTION EXPERIENCE

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Primary CNS Lymphoma (PCNSL) in immumocompetent individuals is rare but the incidence is steadily rising. Conducting clinical trials with this population is challenging and there is no consensus on how to best treat this disease. Several treatment approaches including chemotherapy and radiotherapy have been used in therapy of PCNSL. We report our experience with high dose methotrexate (HD-MTX) in combination with the anti-CD 20 monoclonal antibody, rituximab, in therapy of immunocompetent patients with PCNSL. METHODS: A retrospective chart review of patients treated at our institution over the last several years was conducted after Institutional Review Board approved the study. All patients enrolled received HDMTX at 8 gm/m^2, every 14 days for induction until complete response (CR) was seen, then 2 more cycles every 14 days for consolidation followed by monthly treatments in the maintenance phase. Rituximab was provided for the first 8 weeks of therapy, weekly at 375 mg/m^2. The dose of HDMTX was adjusted based on the patient's creatinine clearance. Each dose of HDMTX was operationally defined as one cycle. RESULTS: We identified 13 patients that met study criteria: six women and seven men with the median age of 66. In 10 (77%) patients, the diagnosis was achieved by biopsy of the intracranial lesion; in two, by resection and in one, by CSF analysis alone. None of the patients had systemic involvement. We provided 117 cycles of HDMTX. Eighty four percent of patients experienced radiographic response: six patients (46%) achieved complete response and five (38.4%) partial response. The longest observed duration of response was 23 months and the shortest 2 months, however in the majority of patients, progression has not occurred at the time of data analysis. There were 2 deaths in the study cohort. Major side effects included transient transaminitis, renal insufficiency and fatigue. None of the patients suffered rituximab associated allergic reaction. CONCLUSIONS: Therapy with HDMTX and rituximab in patients with PCNSL offers high response rate. Therapy is well tolerated and responses are durable allowing for deferment of radiotherapy if needed. The optimal treatment regimen including the number and frequency of rituximab doses and the duration of the maintenance therapy with both HDMTX and rituximab remains unknown and should be studied in a prospective randomized trial.

P.262*. SALVAGE IMMUNO-CHEMOTHERAPY WITH A COMBINATION OF RITUXIMAB AND HIGH-DOSE METHOTREXATE FOR PATIENTS WITH PRIMARY CNS LYMPHOMA

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INTRODUCTION: High-dose methotrexate (HD-MTX)-based chemotherapy with whole brain irradiation (WBRT) improves the prognosis of PCNSL. However, up to 30% of patients are refractory to primary therapy and 60% relapse. Fewer than 50% of patients enter a second remission and the 1 year overall survival (OS) is of 35-57%. Thus, novel treatment regimens for relapsed PCNSL are needed. Rituximab (RIT) is a monoclonal antibody that targets the B-cell specific CD-20 antigen. Most PCNSLs express CD20, and RIT has reported efficacy in recurrent PCNSL. Since MTX is much more active than other agents in PCNSL, a MTX re-challenge has been proposed as a salvage strategy for recurrent disease. We report a retrospective evaluation of patients with recurrent PCNSL treated with a combination of RIT and HD-MTX. METHODS: Six patients that relapsed after HD-MTX and WBRT were treated with a RIT-HD-MTX regimen in a 14-day cycle. If a CR was obtained, the patient was then treated with RIT-HD-MTX or HD-MTX in a two-month cycle. RESULTS: At the start of the RIT-HD-MTX, the median age was 59.5y (range 49-69). Four patients achieved a CR and two achieved a PR, for an objective response rate of 100%. Patients with PR were further treated with temozolomide. One CR patient relapsed after 10 months. This patent received RIT-HD-MTX for second salvage and CR was achieved again. At the median follow-up of 22 months, the median progression-free survival (PFS) was 8.9 months, 1y OS was 67%, and median OS was not reached. Grade 3 hepatotoxicity was seen in one patient, grade 3 lymphopenia in one patient, grade 2 hepatotoxicity in 5 patients and grade 2 neutropenia in one patient. CONCLUSION: The RIT-HD-MTX regimen was a safe and effective strategy. Efficacy compared favorably to other salvage treatment options, suggesting RIT-HD-MTX should be considered in patients with recurrent PCNSL.

P.263*. RECURRENT GENOMIC ALTERATIONS IN PRIMARY CNS LYMPHOMA

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OBJECTIVE: Little is known about the molecular pathogenesis of primary central nervous system lymphoma (PCNSL) in immunocompetent patients. Our objective was to identify the genetic changes involved in PCNSL oncogenesis and evaluate their clinical relevance. METHODS: Twenty nine and four newly diagnosed, HIV-negative PCNSL patients were investigated using high-resolution single nucleotide polymorphism (SNPa) arrays validated by real-time quantitative polymerase chain reaction and whole-exome sequencing respectively. Molecular results were correlated with prognosis.

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RESULTS: All PCNSLs were diffuse large B-cell lymphomas, and the patients received chemotherapy without radiotherapy as initial treatment. SNPa analysis revealed recurrent large and focal chromosome imbalances that target candidate genes in PCNSL oncogenesis. The most frequent genomic abnormalities were (i) 6p21.32 loss, corresponding to the *HLA* locus; (ii) 6q loss; (iii) *CDKN2A* homozygous deletions; (iv) 12q12-q22; (v) chromosome 7q21 and 7q31 gains. Homozygous deletions of *PRMD1*, *TOX*, and *DOCK5* and the amplification of *HDAC9* were also detected. Sequencing of matched tumor and blood DNA samples identified novel somatic mutations in *MYD88* and *TBL1XR1* in 38% and 14% of the cases, respectively. The correlation of genetic abnormalities with clinical outcomes using multivariate analysis showed that 6q22 loss ($p = 0.006$ and $p = 0.01$), and *CDKN2A* homozygous deletion ($p = 0.02$ and $p = 0.01$) were significantly associated with shorter progression free survival and overall survival. CONCLUSION: Our study provides new insights into the molecular tumorigenesis of PCNSL and identifies novel genetic alterations, that may be promising targets for future therapeutic strategies.

NEW DEVELOPMENTS IN SURGERY

P.264*. SURGICAL MANAGEMENT OF TUMOURS CAUSING EPILEPSY LOCATED IN ELOQUENT BRAIN AREAS USING FUNCTIONAL NEURONAVIGATION AND INTRAOPERATIVE MR IMAGING

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OBJECTIVE: Intractable epilepsy due to tumours located in eloquent regions is often considered surgically inaccessible because of the high risk of neurological deterioration. Advanced preoperative functional imaging using functional (f-) MRI, MRI tractography and magnetoencephalography (MEG) as well as intraoperative MR imaging might change this estimation. Thus, we retrospectively investigated the management and outcome of tumour patients operated upon for their epilepsy at the Erlangen epilepsy centre using advanced neurosurgical techniques. METHODS: Twenty-two patients (12 female, 10 male, from 16-69 yrs, mean 42.7 yrs) suffering from tumour related epilepsy with lesions located in or close to eloquent brain areas were evaluated preoperatively using fMRI (motor in 5, memory in 1, speech in 15: Broca 7, Wernicke 8), MRI tractography (pyramidal tract in 6, visual tract in 6, arcuate fascicle in 10) and speech-MEG (Wernicke 1, Broca 2). Functional imaging was integrated into intraoperative neuronavigation for biopsy or resection of tumours (7 Gangliogliomas, WHO I; 1 Diffuse Astrocytoma, WHO II; 1 Anaplastic Astrocytoma, WHO III; 1 Papillary Glioneuronal Tumour, WHO I; 2 GBM, WHO IV; 3 DNT, WHO I; 1 Anaplastic Oligodendroglioma, WHO III; 5 Anaplastic Oligoastrocytoma, WHO III; 1 PXA, WHO II). RESULTS: In the 22 tumours located in high risk brain areas, 12 complete resections were achieved (3 after intraoperative MR image update). Furthermore, 5 incomplete resections with significant tumour volume reduction and 5 biopsies were performed. Two high risk lesions were excluded from surgical intervention. They were considered inoperable on the basis of advanced functional imaging. Neurological deterioration was found permanently in 1 patient with lesionectomy near the visual tract. In 82% of the patients (14/17), the outcome in respect to seizure control was quantified as Engel class 1 and in 6% (1/17) as Engel class 2. CONCLUSION: Despite the highly eloquent location of the tumours causing intractable epilepsy, preoperative functional imaging, intraoperative advanced neuronavigation and MR imaging update led to complete resection in more than half of the cases with anacceptable neurological morbidity and excellent seizure control.

P.265*. INTRAOPERATIVE IDENTIFICATION OF MOTOR CORTEX USING MULTIMODAL NEURONAVIGATION IN SURGERY OF INTRA-AXIAL BRAIN TUMORS

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OBJECTIVES: Accurate intraoperative identification of the eloquent cortex is an essential for successful surgical excision of intra-axial tumors involving sensorimotor area. METHODS: Total of 130 patients (71 males, 59 females, mean age 43.6 years, range 17-69 years) underwent preoperative MRI, MRA, MR-tractography, fMRI and SPECT studies. Brain tumors located in sensorimotor area in 105 patients and in close to central region in 25 patients. The preoperative planning and tumor microsurgery resection were carried out using the multimodal neuronavigation system (Medtronic StealthStation TREON Plus). The three-dimensional models were reconstructed from MRI data during the surgical planning and composed of tumor, cerebral hemispheres with marked motor areas, corticospinal tracts, cortical surface vessels and ventricles. RESULTS: The surgical planning with multimodal neuroimage data three-dimensional reconstruction of anatomical and functional structures reveals spatial relationship between eloquent areas and tumor margins. The accurate intracranial orientation was performed with using of cerebral surface veins as reliable landmarks for transcortical approach and control of accuracy of neuronavigation system. A gross total or nearly gross total tumor resection was achieved in 64 (49.2%) patients, subtotal resection in 60 (46.2%), partial resection in 6 (4.6%). Gliomas were in 112 (86.1%): glioblastomas in 32 (24.6%), anaplastic gliomas in 42 (32.3%), diffuse gliomas in 38 (29.2%). Metastases were in 18 (13.9%). After surgery 78 (60.0%) patients had improved KPS score, 47 (36.2%) were stable, and 5 (3.8%) patients had lower KPS score. Median KPS score increased from 67.7 to 85.0. CONCLUSION: The application of multimodal neuronavigation for preoperative planning and intraoperative guidance allows to perform maximal resection of intra-axial tumors in eloquent areas with low risk of postoperative neurological morbidity.

P.266*. INITIAL EXPERIENCE WITH AN INTRAOPERATIVE MAGNETIC RESONANCE EQUIPMENT IN THE SPANISH PUBLIC HEALTH CARE SYSTEM

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BACKGROUND: Intraoperative MRI (iMRI) is considered in our days the gold standard over other intraoperative imaging modalities such as ultrasound or iCT. It provides a precise judgment of surgical performance with the patient still in the operating room and overcomes brain shift. Low field systems are more affordable and offer acceptable quality images. OBJECTIVE: To report on our experience in using the first low-field intraoperative iMRI system Medtronic PoleStar® N-20 available in the Spanish Public Health Care System. Patients and methods. Between June 2011and January 2012, twenty-one patients were operated on with the aid of the PoleStar® N-20 iMRI system, which is a compact iMRI scanner with a field strength of 0.15T. There were 15 patients harboring brain tumors and 6 with sellar region lesions. Surgeries were performed as standard micro-neurosurgical procedures using regular instruments and techniques (ultrasonic aspirator, neuroendoscope, bipolar cortical stimulator), and two patients underwent awake procedures for brain mapping. An initial iMRI study with or without contrast was performed in all patients after positioning. When the neurosurgeon believed that tumor resection was achieved, a second scan was done. Surgical goal was maximal safe resection. All patients underwent high-field MRI at 1.5T or 3T with and without contrast before surgery and within 5 days after surgery to detect residual tumor. The comparison between iMRI and postoperative images was carried out in a blinded fashion. RESULTS: The overall time spent in the operating room was increased by a mean of 118 min. Patient positioning resulted especially complex in awake surgeries. Supine position was used in 19 cases. Two patients with tumors in the occipital lobe and posterior fossa were operated on in prone and lateral positions. Intraoperative imaging led to extended tumor resection in 6 (28.5%) patients. Complete tumor resection could be achieved in 15 (71.4%) cases. After comparison between the last iMRI study and the postoperative MRI, 2 (9.5%) cases were considered "false negative" as iMRI images did not show residual tumor that was evident on the postoperative study. Fifteen (71.4%) cases were considered "true negative" as iMRI and postoperative images were concordant with respect to the absence of residual tumor. The remaining 4 (19.1%) cases were found to be "true positive" as iMRI and postoperative controls were concordant with respect to the existence of residual tumor. We did not have any "false positive" case. Sensitivity 66.6%, specificity 100%. CONCLUSIONS: Our data show that sensitivity and specificity of low-field intraoperative PoleStar® N-20 system for detecting residual tumor seems acceptable. Its practicality, ease of execution and relative low cost compared to high field equipments, make it a helpful and valuable tool in modern neurosurgery.

P.267. TOTAL SPONDILECTOMY IN A C2 SPINE TUMOR USING A PEDIATRIC CUSTOMIZED VERTEBRAL BODY PROSTHESIS: TECHNICAL CASE REPORT

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Indications for complete C2 spondilectomy are uncommon and mainly limited to the treatment of those tumors in which radical resection offers a

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clear prognostic advantage. Surgeons are reluctant to perform this operation because it means dealing with critical neural and vascular structures and a complex reconstruction at the C1-C2 level. We report the case of a 6 year-old girl who presented with a posterior cervical painful mass and movement limitation. Radiological evaluation showed a huge C2 tumor affecting and destroying the whole vertebra. In a first-stage a posterior midline approach allowed subtotal tumor resection, releasing of neural structures and both vertebral arteries and an occipitocervical fusion. Pathology was diagnostic for aneurysmal bone cyst. As this pseudotumoral lesion shows high recurrence rates in cases of incomplete removal, a second surgical procedure was performed 5 weeks later. An anterior transoral approach was done with radical removal of the infiltrated C2 vertebral body. To obtain a stable anterior support, a customized titanium mesh-plate was used. It offers redistribution of the axial load of both C1 lateral masses to the C3 vertebral body and a secure screw fixation. The implant was specifically made for our pediatric patient, based on an original adult design. This constitutes the first case in which such prosthesis has been adapted and implanted in a child. Our patient did very well; she completely recovered without any neurological deficit. A total tumor resection could be demonstrated in the postoperative studies. There has been no recurrence after 6 months of follow-up. Although complete C2 spondilectomy is technically demanding, it offers a clear advantage in terms of tumor control and patient recovery in selected cases. A customized C2 vertebral body prosthesis can be adapted for pediatric use, making surgery easier and safer, enhancing the biomechanical strength and stability of the construction.

P.268*. DISCORDANCE BETWEEN OPERATIVE ELECTROSTIMULATION MAPPING AND PRESURGICAL NEUROIMAGING OF LANGUAGE AND MOTOR FUNCTION: A META-ANALYSIS

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INTRODUCTION: Mapping of brain functions for resective brain surgery intends to preserve functional integrity of patients and to maximize extent of resection of diffuse infiltrating glioma. This study evaluates the agreement between presurgical neuroimaging using functional MRI, Magnetic Source Imaging (MSI) and Diffusion Tensor Imaging (DTI) and operative electrostimulation mapping for the localization of motor and language function. METHODS: A random effects meta-analysis based on 50 publications, which qualified for selection criteria, evaluated the concordance, false-positive, and false-negative rate of sites identified by presurgical neuroimaging in relation to operative electrostimulation mapping. RESULTS: The summarized concordance for localization of motor function was 0.85 (0.75-0.93) for fMRI, 0.86 (0.48-1.00) for MSI, and 0.89 (0.70-1.00) for DTI of the corticospinal tract. The summarized concordance for localization of language function was 0.49 (0.14-0.84) for fMRI, 0.99 (0.93-1.00) for MSI, and 0.85 (0.65-0.98) for DTI of the arcuate fasciculus. Heterogeneity of concordance was considerable between the publications reporting on motor function: 77% for fMRI, 89% for MSI, and 91% for DTI, as well as on language function: 98% for fMRI, 0% for two studies on MSI, and 85% for DTI. CONCLUSION: Presurgical neuroimaging to localize motor or language function is not a valid substitute for operative electrostimulation mapping and should be considered complementary at best. In addition, the variation in task paradigms, and applied recording and analysis protocols warrants standardization of presurgical functional mapping.

P.269*. THE IMPACT OF INTRAOPERATIVE RESECTION CONTROL IN BRAIN TUMOR SURGERY

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OBJECTIVE: Recent evidence suggests that the extent of resection (EOR) is a prognosticator for patients harboring gliomas. The use of both, intraoperative MRI- (iMRI) and 5-aminolevulinic acid (5-ALA) has been proven to improve the extent of resection in contrast-enhancing malignant glioma surgery. Our aim was to compare iMRI with 5-ALA fluorescence-guidance in order to maximize EOR in patients with contrast enhancing tumorous lesions. METHODS: 25 patients with known or suspected high-grade gliomas undergoing intended gross total resection (GTR) were included in a prospective study. All patients received 20mg/kg 5-ALA prior to surgery. When GTR was thought to be achieved, an iMRI scan was performed, and blue light turned on, to search for unintentionally remaining tumor tissue. IMRI findings were directly compared with intraoperative fluorescence findings in every patient. Histological examinations of the bulk of the tumor as well as any additionally resected tissue were performed and classified as normal tissue, infiltration zone, or solid tumor. All patients underwent early postoperative high-field MRI to determine EOR. Patient overall survival (OS) was determined by Kaplan-Meier analysis. RESULTS: Postoperative MRI showed GTR in all patients. In 10 patients (40%), iMRI and fluorescence unequivocally had not shown residual tumor intraoperatively. In 15 patients (60%) resection was continued due to iMRI and/or fluorescence findings. In 10 out of these (66.7%), iMRI and 5-ALA findings were inconsistent regarding residual tumor. Histological examination ruled out false positive findings in all additionally resected specimens. Sensitivity and specificity to detect residual tumor tissue were 66.7% and 100%, respectively, for both iMRI and 5-ALA. The accuracy of these surgical tools to detect residual tumor was 80.0% each. The majority of additionally resected specimens due to iMRI findings were classified as solid tumor, while they represented infiltration zone more often than solid tumor in specimens additionally resected due to 5-ALA findings. Complications occurred in 3 patients (12%) and were not attributable to continued resection ($P = 0.25$). Median OS for the entire cohort was 18.8 months. CONCLUSIONS: IMRI and 5-ALA are complementary techniques in brain tumor surgery. Although iMRI detected residual solid tumor more frequently than 5-ALA, optimum results can only be achieved through combined use of these surgical tools.

P.270*. THE DETERMINATION OF INTRA-OPERATIVE NAD(P)H REDOX STATUS IN PATIENTS WITH BRAIN TUMOURS

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INTRODUCTION: The significance of derangements in cellular redox related metabolic pathways to the development and behaviour of cancers has been highlighted in a number of recent reviews and is of increasing interest to brain tumour researchers. Nicotinamide adenine dinucleotide (NAD+) and NAD phosphate (NADP+) are involved in numerous cellular redox reactions, the failure of which is associated with the growth, chemoresistance and invasion of malignant cells. For example, spontaneous point mutation in the gene for the cytosolic enzyme isocitrate dehydrogenase 1 (IDH1) which have been shown to confer a significantly improved prognosis in 12% of patients with malignant glioma results in the diminished availability of NAD(P)H and the tumour cellular capacity to generate NADH by 48%. [1,2]. We describe a novel method of intra operative measurement of NADH/NADPH redox potentials in a number of CNS tumours correlating these with histological diagnosis, IDH1 mutational status and grade with comparisons made with normal tissue. METHODS: Patients with radiologically confirmed intracranial CNS tumours undergoing respective surgery were recruited. Intra-operative tumour samples were analysed to establish their NAD(P)H redox status using a novel combined gated pulse fluorescent excitation and nanosecond time-resolved fiberoptic fluorescence detector. Samples also underwent histological characterization and analysis for IDH1 genetic mutation. RESULTS: Significant differences were noted in NAD(P)H redox between the tumour types examined (High and low grade glial tumours, meningioma, intracranial metastases, haemangioblastoma and schwannoma) Significant differences were also noted between grades of glial tumours as well as grade one and atypical meningiomas. Characterization of tumour IDH1 status awaits confirmation and will be available for presentation. DISCUSSION: Preliminary data from this ongoing study confirms proof of principle with SD values at reasonable levels and correlation of NAD(P)H redox status and histological diagnosis and grade. Once established this technique could have the potential to give intra-operative prognostic information and the possibility of exploring new therapies whose mechanisms of action would target redox reactions integral to the behaviour of a number of intracranial tumour types. 1. Parsons DW, et al. 2008, Science. 321(5897):1807-12. 2. Bleeker FE, et al. Hum Mutat. 2009;30:7-11.

P.271*. BRAIN MAPPING WITH INTRA-OPERATIVE NEUROPHYSIOLOGICAL MONITORING AND MINIMALLY INVASIVE CRANIOTOMIES: ARE THESE TWO TECHNIQUES MUTUALLY EXCLUSIVE?

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INTRODUCTION: Intra-operative neurophysiological monitoring and brain mapping techniques are nowadays the gold standard for surgical resection of gliomas located within or in proximity of eloquent areas. Brain mapping usually requires the exposure of a large area of brain cortex in order to identify the different eloquent sites (e.g. primary motor strip, speech arrest sites). Thus, relatively large classic fronto-temporal craniotomies are generally performed. Nevertheless, in recent years the use of small craniotomies targeted on the tumor has gained popularity thanks to the diffusion of Neuronavigation systems and to the low morbidity rates associated with shorter surgical procedures and reduced anesthestic drug administration. Aim of this study was to review our initial experience which combines extensive neurophysiological monitoring and small craniotomies. Length of surgical time, intra-operative and post-operative complications, length of stay, extent of resection rate and the neurological outcomes were assessed. PATIENTS AND METHODS: Twenty-two consecutive patients (15 Males, 7 Females; Median Age 56 years, range 32-77) underwent surgery with brain mapping and intra-operative neurophysiological monitoring for resection of a glioma in eloquent location under asleep-asleep (17 patients) or asleep-awake (5 patients) anesthesia. Thirty-two percent of patients had already received a previous operation (recurrent tumors). Pre- and post-operative assessment included in-depth neuropsychological evaluation. Tumor histology was the following: 13% grade II, 23% grade III, 64% grade IV gliomas. The bone flap was tailored to the size of the tumor; no cortex other than that which was strictly necessary for tumor resection was exposed. The intra-operative neurophysiological monitoring included: EEG, SSEP, transcranial MEP (9 patients) and/or cortical MEP (16 patients), ECoG; direct electrical stimulation (DES) was performed using bipolar and monopolar probes. RESULTS: Median surgical time was 240 minutes (range 120-360). Intra-operative complications included 5 seizures (1 requiring pharmacological treatment, 4 rapidly regressing after cold irrigation) and 1 electrical seizure. Post-operative complications were the following: 1 generalized seizure, 2 partial seizures, 4 infections (2 urinary tract, 2 pneumonias). Neurological examination was unchanged/improved in 19 out of 22 patients at 1 month follow-up. Extent of resection was total in 14 patients, subtotal in 4 and partial in 4. Median post-operative stay was 8 days (range 3-18). CONCLUSIONS: In our preliminary experience on 22 patients with gliomas in eloquent areas, a minimally invasive tumor targeted craniotomy supported by extensive neurophysiological monitoring and brain mapping achieved promising results in terms of extent of resection and neurological outcomes.

P.272*. 5-ALA GUIDED RESECTION OF MALIGNANT GLIOMA: A SINGLE INSTITUTION EXPERIENCE

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INTRODUCTION: Malignant gliomas are the most unfavourable brain tumours. Recent evidence suggests that extensive tumour removal is associated with better survival. The current standard treatment is considered radical as possible resection of the contrast-enhancing tumour tissue, followed by adjuvant treatment with radiotherapy and chemotherapy. As it appears difficult to distinguish between infiltrating tumour and normal tissue, especially in recurrent tumours, gross total removal becomes harmful. Techniques to intraoperatively visualize the borderline tumour are helpful. More recently, fluorescence guidance has taken advantage of intrinsic metabolic and structural changes that occur within malignant gliomas by exploiting the eme biosynthetic pathway and a natural biochemical in that pathway, 5-aminolevulinic acid (5-ALA). METHODS: Since the end of 2009, in our Institute 35 patients were operated on using fluorescence guided tumour resection. Preoperatively, all enrolled patients had MRI showing contrast enhancing lesions. MRI within 72 hours after surgery and thereafter at 3-month interval was performed. 20 patients were newly diagnosed tumour, 15 were recurrent malignant glioma. An oral dose of 20 mg 5-ALA /kg body weight was administered to each patient. By a NC4 OPMI Pentero operating microscope (Zeiss), enabled switching from xenon light to violet-blue light for visualizing fluorescence, the surgical resection was performed. Histology was in 30 glioblastoma (1 gliosarcoma), in 3 anaplastic oligodendroglioma, in 1 oligodendroglioma I WHO and in 1 pleomorphic xanthoastrocytoma. All the patients, as first line treatment, were submitted to radiotherapy and chemotherapy; in recurrent tumours second and in some cases third line treatments were administered. The follow-up ranged from 2 years to 8 months. RESULTS: In all cases the yellow fluorescence due to 5-ALA in cortical vessels was seen. In 30 glioblastoma, 2 anaplastic oligodendroglioma and 1 xanthoastrocytoma the tumour tissue showed intraoperative red fluorescence. Especially in recurrent tumours, the fluorescence-guided surgery was helpful to identify, inside the gliotic tissue, some areas with active tumour from perilesional "healthy" brain. Furthermore, after surgery no relevant neurological deficit caused by 5-ALA guided resection were observed. Early postoperative MRI confirmed gross total resection without contrast enhancement in 80 % of patients. At the follow-up 24 patients are still alive. CONCLUSIONS: The 5-ALA was helpful to localize the tumour on the cortex and realize extended resection of infiltrating tumour, mainly in recurrence. Patients affected by glioblastoma are elective for this technique. Extended resections by 5-ALA fluorescence guide do not impair neurological functions and can impact on the overall survival of patients affected by malignant glioma.

NEW DEVELOPMENTS IN RADIOTHERAPY

P.273*. EFFECT OF BEVACIZUMAB ON RADIATION NECROSIS OF THE BRAIN

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PURPOSE: Because blocking vascular endothelial growth factor (VEGF) from reaching leaky capillaries is a logical strategy for the treatment of radiation necrosis, we reasoned that bevacizumab (Bev) might be an effective treatment of radiation necrosis. In this study, the authors evaluated a 6-cycle schedule of Bev for the treatment of radiation necrosis. PATIENTS AND METHODS: Eleven patients with radiation necrosis (6 Glioblastoma, one anaplastic astrocytoma, 3 metastatic brain tumor, and one primary CNS lymphoma) were treated with Bev on a 5 mg/kg/2-week schedule. Radiation necrosis was diagnosed in 11 of these patients on the basis of ^{11}C methionine (MET)-PET and/or biopsy. MET-PET, **11C-choline (CHO)-PET** and MRI studies were obtained before treatment and after bevacizumab treatment completion. On PET scans, the ratio of tumor tissue to normal tissue (T/N ratio) was defined as the mean counts of radioisotope per pixel in the tumor divided by the mean counts per pixel in normal gray matter. RESULTS: In 9 of 11 patients, neurological dysfunction was remarkably alleviated after Bev therapy. Post-treatment MRI performed after Bev therapy showed a significant reduction in T2-weighted abnormalities and T1-weighted post-contrast abnormalities. **Post-treatment PET showed a significant reduction T/N ratio of MET, and T/N ratio of CHO.** There was no severe adverse effect by Bev therapy. CONCLUSIONS: We demonstrated the clinical effectiveness of Bev therapy for the patients of radiation necrosis. We conclude that Bev can reduce radiation necrosis significantly by decreasing capillary leakage and associated brain edema.

P.274*. PHOTON ACTIVATION THERAPY OF RAT GLIOMA

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Photon activation radiotherapy (PAT) relies on the administration of a drug containing a high-Z element prior to external irradiation with x-rays. If the drug is targeted to tumour cells, this can potentially yield a very large therapeutic absorbed dose ratio between tumour and normal healthy tissue. In this work, we have studied PAT with monoenergetic synchrotron radiation and intracranial administration of stable thallium on Fischer rats carrying RG2 rat glioma. The energy of the radiation was optimized to maximize the local energy deposition enhancement, depending on the cellular localisation of thallium uptake. Seventy-five animals were divided into three groups receiving treatment with radiation at different energies; $E = 50$ keV, $E = 85.5$ KeV, and 86.5 keV (which is just below and above the K-edge of thallium). The absorbed dose was 10 Gy or 15 Gy. One control group was treated with radiation only, one with thallium only, and one group received no treatment at all. The longest mean survival time, which was obtained for the rats treated with thallium in combination with radiation to 15 Gy at energy $E = 50$ keV, was 29.3 days, 63% longer than for the untreated controls. However, at the higher energy there was no statistically significant difference in the mean survival time, neither between the groups treated with or without thallium, nor between the groups treated with energy below or above the K-edge. According to these results, it is not plausible that the microscopic distribution of thallium is highly concentrated to the cell nucleus. This is in contradiction to previous assumptions based on the evidence for the enhanced toxicity of radioactive thallium.

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P.275*. RE-IRRADIATION WITH AND WITHOUT BEVACIZUMAB IN RECURRENT OR PROGRESSIVE HIGH-GRADE GLIOMAS (HGG): RETROSPECTIVE ANALYSIS OF 13 PATIENTS

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INTRODUCTION: Treatment of recurrent or progressive high-grade glioma (HGG) is a real clinical challenge. Especially younger patients receive several lines of surgery and chemotherapy to treat disease progression. As therapeutic options in recurrent HGG are limited new effective strategies are urgently needed. Several reports with different re-irradiation (re-RT) approaches (radiosurgery, 3-D conventional radiation techniques) with and without chemotherapy demonstrated usefulness of a second radiotherapy in relapsing HGG. More recently, a prospective trial of hypofractionated stereotactic radiotherapy (SRT) in combination with bevacizumab (Bev) showed promising results in this situation. METHOD: We retrospectively reviewed 13 patients treated with re-RT including 10 patients additionally receiving bevacizumab (10mg/kg every 14 days) before, concomitant and after second radiation until progression. 3-D conformal radiation at retreatment consisted of 39-50.4 Gy. RESULTS: Between 2009 and 2011 we treated 9 men and 4 women with a median age of 44 years suffering from progressive HGGs (6 GBM, 3 sGBM, 2 AA, 1 AOD) with re-irradiation. The median cumulative physical radiation dose was 101.6 Gy (range 81.6 to 110.4 Gy). 1st-line radiotherapy doses varied according to different histology at initial diagnosis (range 40-60 Gy). Three patients didn't receive Bev according to contraindications. One patient was treated with Bev and temozolomide at the time of re-RT. Median time between prior RT and re-RT was 44 months (range 6 to 388 months). Median PFS and OS after re-RT were 5.1 and 8.0 months, respectively. Median OS from first diagnosis was 50.5 months and median time form first diagnosis to re-RT was 41.8 months. Four patients are still alive. Side effects consisted of one asymptomatic radiation necrosis (10 month after re-RT), one asymptomatic cerebral bleeding (7 month after re-RT), one epistaxis and one nephrotic syndrome due to long term Bev treatment before initiation of re-RT. CONCLUSIONS: Bearing the caveats of retrospective studies in mind we conclude, that fractionated 3-D conformal radiation with and without Bev up to 50.4 Gy and a cumulative re-irradiation dose as high as 110.4 Gy is feasible (provided a minimal time between prior RT and re-RT of 6 months) for the treatment of recurrent or progressive HGG. Median PFS and OS are comparable to former re-irradiation studies with more technical advanced radiation procedures like SRT and radiosurgery. Therefore, an important advantage of our approach is the fact, that re-irradiation for HGG with conformal radiation can be applied in every radiotherapeutic unit. Re-irradiation with or without Bev as a salvage treatment should be investigated against 2nd line-therapies in prospective clinical trials.

P.276*. ROLE OF 11C-METHIONINE PET/CT FOR RADIOTHERAPY PLANNING OF PATIENTS AFFECTED BY PRIMARY BRAIN TUMOUR

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PURPOSE: 11C-MET is a radiolabelled aminoacid successfully utilized in PET imaging of primary and metastatic brain tumours. So far, very limited evidence concerns its utilization for radiotherapy planning. Thus the aim of our study is that to investigate its role in patients affected by rimary brain tumours in this clinical setting. METHODS: we enrolled 21 patients (M:F = 14:8; mean age 53.2yrs) affected by a histologically proven primary/relapsed gliomas, who were addressed to our Institution for radiotherapy. Almost half of them (10/21) had already been treated and presented during relapse. In all cases dedicated MR, CT and MET-PET were scheduled before treatment and performed according to standard procedures. GTV was outlined on CT images fused to MR (GTV-MRI/CT), on MET-PET positive regions only (GTV-PET), and final volumes were calculated by using PET/CT/MRI co-registered images. Optimal radiation dose required was 60Gy. In 7 patients a contemporary Chemo/radiotherapy regimen was administered. The mean observational period was 6months, up to 22months. In 13 patients a post-radiotherapy evaluation was performed and of these we calculated PFS and OS. In 3 patients progression/relapse was defined within 7 months, whereas other 3 patients deceased within 2 months. Statistical analysis was performed on clinical and instrumental data in order to define correlation and prognostic value of different parameters. RESULTS: in19 out of 21 patients a GTV-PET could be defined (mean 18,3cc), which in 14 cases (73,7%) determined a modification of the GTV-MRI/CT (mean 58.79cc). Malignant lesions presented a SUVmax = 3.37 (range1.60-5.17) and a SUVratio(SUVmax/SUVnormal) = 2.43 (range1.53-3.26). There was a significant correlation between tumour grade and SUVmax ($p < 0,0001$). In 10/21 cases the tumour was multifocal, of which 3/10 bilateral. The overall volume change, according MET-PET, was 139,58cc (mean 6,65cc), corresponding to 11,2% of total GTV. The ROC-analysis defined an optimal SUVmax cut-off point $< =2,7$ (Sens.100%; Spec.90%), whereas for SUVratio $< =1,73$ (Sens.100%; Spec.81,3%). Univariate analysis on PFS documented a significant correlation for SUVmax cut-off ($p = 0,0077$) and SUVratio cut-off ($p = 0,0301$), but not for tumour grade ($p = 0,7961$), previous relapses ($p = 0,1573$), tumour multifocality ($p = 0,5271$) and concomitant chemo/radiotherapy ($p = 0,5749$). CONCLUSIONS: our data demonstrate that MET-PET has a significant impact on radiotherapy planning of patients presenting with primary/relapsed gliomas. Moreover, metabolic characteristics of the tumours appear better correlated to patients outcome, compared to other clinical parameters.

P.277*. THE PROGNOSIS OF PATIENTS WITH GLIOBLASTOMA MULTIFORME (GBM) REMAINS ALMOST UNCHANGED, DESPITE THE PROGRESS IN THE DIFFERENT MODALITIES OF TREATMENT OF CNS TUMORS

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INTRODUCTION: Now a day, the importance of hipofractionated radiotherapy are developing to shorten the duration of 6 weeks of standard radiation as an attempt to prevent the repopulation of tumor cells. We analyze our preliminary results using hypofractionated three-dimensional radiotherapy treatment regimen using a concurrent boost for the irradiation of glioblastoma multiforme. Treatment plans were designed to investigate the efficacy, toxicity, and control of the neurological symptoms in an historical cohort. MATERIAL AND METHODS: Between January 2010 and May 2011 five patients with glioblastoma multiforme were treated with partial surgical resection. All of them had an ECOG ≤ 2. We planned three progressively smaller volumes of irradiation: target A (GTV), target B (CTV-1) and target C (CTV-2). The radiotherapy was performed with virtual simulation and three-dimensional planning, following ICRU 62. A dose distribution to the three targets was obtained using biological effectiveness criteria with a simultaneous integrated boost (SIB). We considered a first volume of treatment called target A, consisting of GTV + margin of 0.5 cm. which was treated with a dose of 66 Gy / 3 Gy session / 5 sessions per week (standard dose of 75 Gy equivalent or effective biological dose GY5 105). A second volume of treatment called target B, consisting of GTV + margin of 1.5 cm, which was treated with a dose of 55 Gy Gy/2.5 session / 5 sessions per week (effective biological dose GY5 82.5). A third volume of treatment called target C, consisting of GTV + margin of 2.5 cm, which was treated with a dose of 44 Gy / 2 Gy session / 5 sessions a week. The total duration of treatment was 23 days. RESULTS: Examination of motor function, sensory and cerebellar function after irradiation was not diminished in relation to its status prior to treatment. There were no changes in the intensity of seizures or signs of intracranial hypertension. An increase in the dose of corticosteroids was necessary in two cases. There were not any impaired of quality of life during the treatment. CONCLUSIONS: 1. Although this is a small series of cases, the progression-free survival of patients, treated with hypofractionated technique with simultaneous boost, is similar to our historical cohort treated with standard therapy. 2. There were no significant acute or late toxicity in relationship of the treatment provided. 3. The reduction in number of treatment's days improves the quality of life of the patients and produces an important reduction of the cost of radiotherapy

P.278*. DEVELOPMENT OF TARGETED NANOMEDICINE FOR GLIOBLASTOMA THERAPY

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Glioblastoma is the most common primary malignant brain tumour in adults. Despite recent therapeutic advances, the treatment of glioblastoma remains inadequate. Moreover, present evidences suggest that; glioblastoma contains tumour-initiating cancer stem cells. They are resistant to the conventional radiation and chemotherapy which results in tumour recurrence. Gold nanoparticle mediated enhanced X radiation therapy can be a viable solution in this regard. Because of its high atomic number, gold preferentially absorbs kV X- rays compared to the soft tissue, resulting in the emission of ionizing Auger electrons. The enhanced free radicals generated by the gold nanoparticle under this condition in combination with chemotherapeutic

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drug can lead to the effective demolition of the malignant tissue. In the current project, a novel nanoconjugate made of human serum albumin and polyethylenimine capped gold nanoparticle is developed. DLS and UV-Visible spectrophotometric studies indicate that the nanoconjugates are extremely stable at physiological pH. Cell viability assay showed that the nanoconjugates are nontoxic. *In vitro* uptake of this nanosystem by glioblastoma tumour-initiating cells is proved by confocal microscopy and transmission electron microscopy. Growth curve, DNA damage assay and apoptosis assay have proved the *in vitro* radiosensitization capacity of this nanoconjugate in glioblastoma tumour-initiating cells. Future studies will analyze the potential of this nanosystem in combination with chemotherapeutics for glioblastoma therapy. Moreover, by functionalizing the nanosystem with appropriate targeting moieties this project will try to develop more effective tumour-initiating cell targeted therapy for glioblastoma.

P.279*. CYBERKNIFE RADIOSURGERY IN THE TREATMENT OF BENIGN INTRA OR PARA-SPINAL LESIONS

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INTRODUCTION: For patients with benign intra or para-spinal lesions, the first option is surgery. But, in many cases, due to the type of lesion or to the risk of morbidity, remnants are left behind or recurrences occur. Radiosurgical treatment of these lesions offers a new alternative after surgery or, as a first line treatment in those cases where high risk surgery is expected. We analyze our over five year experience in the treatment of these lesions with the CyberKnife system. MATERIAL AND METHODS: Between November 2006 and February 2012, 29 patients with different types of benign intra or para-spinal lesions have been treated and followed in our Unit. In 20 cases the lesions were spinal, 9 of them in the cervical region. Most lesions were meningiomas (6), schwannomas (9) including 2 neurofibromatosis patients, and paragangliomas (5). The mean age was 49 years (range: 26-83). The mean volume of the lesions was 24.88 cm^3 (range: 0'21 -160). In four cases multiple lesions were treated. The most frequent symptom was pain (52%). Sixteen patients had previous surgeries (mean number of surgeries: 2. Range: 1-4). Four patients had also received previous radiotherapy, and two the lesions had been embolized. Treatment was performed with the CyberKnife system with localization control and X-sight tracking. The administered dose varied in relation to the fractionation regimen (1 to 5 sessions) and to the type of lesion. RESULTS: The mean follow up is 33.56 months (range: 15 - 46). A radiological stabilization (with MRI imaging) occurred in 74% of cases, a reduction in the size of the lesion in 21%, an only in one case there was a tumor progression. Sixty-nine % of patients improved their clinical condition, and only one had a recurrence of pain after four months of good response. The rest remain stable. To date no toxicity or added neurological symptoms has been recorded. The 2 treated arterio-venous malformations have not presented new bleeds. CONCLUSIONS: Cyberknife treatment seems to be an adequate treatment alternative for intra-spinal lesions not included in the cord, as well as in other extra-cerebral lesions where surgery was not considered or in cases of incomplete resections. It is a simple and fast treatment, with good results in relation to control and toxicity. Long term follow-up is required to confirm these preliminary results, although they are supported by the more extensive experience of other centers where this technique is available.

P.280*. DUAL INHIBITION OF PI3K AND mTOR LEADS TO GLIOMA RADIO-SENSITIZATION

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INTRODUCTION: Inhibition of the PI3k-Akt-mTOR axis has been shown to be an excellent target for radio-sensitization in many tumor models *in vitro* and *in vivo*. Glioblastoma Multiforme (GBM) is the most common primary brain tumor in adults mostly treated with combined regimen of radiotherapy and chemotherapy post-operatively. A common feature of GBM is an augmented RTK receptor survival pathway which includes the PI3k-Akt-mTOR axis. Targeting this pathway in glioma seems to be an attractive therapeutic approach. MATERIALS AND METHODS: Studies were performed on a panel of established human glioma cell lines (U251, U87, T98, D384). The IC^{50} of the drugs on cell viability was assessed by SRB assay. The radiosensitizing effect was determined by clonogenic survival assay. For this purpose cells were treated for 24h with both drugs (dose range: 1-100 nM) and irradiated (0 - 8 Gy). Phospho-Akt protein levels were determined by Westernblot. RESULTS: Both drugs inhibited the PI3k-pathway which resulted in radio-sensitization. In the combination of the two drugs an equal radio-sensitizing effect was found at a 10-fold lower concentration, where the drugs were ineffective by itself. At these concentrations the plating efficiency of the cells was not affected. The radio-sensitizing effect matched with p-Akt expression. CONCLUSION: PI3k/mTOR pathway inhibition leads to radiosensitization in human glioma cell lines. Because these effects were achieved at low drug concentrations, the combination of these two drugs with radiotherapy offers a promising perspective in glioma therapy. This research is supported by the Dutch Cancer Society, Grant No. VU2010-4874.

P.281*. APPLICATION OF IMRT TECHNIQUE IN TREATMENT OF MALIGNANT GLIOMAS. ASSESSMENT OF TREATMENT TOLERANCE

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BACKGROUND: Assessment of tolerance of combined modality therapy of patients with malignant gliomas irradiated using IMRT technique. We compared dose distribution in IMRT and conformal 3D treatment plans. MATERIALS AND METHODS: Between 2009 and 2011 in the Oncology Center in Krakow 39 patients with malignant gliomas received combined modality treatment. Mean age was 52 years (range 28 - 72 years). All patients were in good performance status (WHO 0-1). There were 32 patients with glioblastoma multiforme and 7 with anaplastic astrycytoma. Twenty two patients underwent complete resection and 17 partial resection. Patient were irradiated using IMRT technique with a total dose of 60Gy in 30 fractions. All patients concurrently received temozolamide 75mg/m2. In all patients we performed additional plans using 3D conformal radiotherapy (3D-CRT) techniques and compared with IMRT plans. The 3D-CRT plans were prepared using 3-4 fields and IMRT plans consisted of 7-8 fields. The primary objective was to treat the planning target volume and to minimize the dose to organs at risk (OAR). Volumetric analysis, target coverage and conformity of prescribed doses were used in plan comparison. RESULTS: Treatment tolerance was vary good in all patients. Only 9 patients needed steroids during treatment. Adjustment of the dose distribution to the target volume was improved and the critical structures were better spared in the IMRT plans than in 3D-CRT plans. For all patients the mean dose and the maximum dose to OAR were significantly reduced in IMRT plans. With respect to target volume, IMRT technique reduced the maximum dose while increasing the minimum dose, resulting in improved conformity. In same patients with tumors located very close to OAR it was impossible to give 60Gy for target volume with 3D-CRT technique because of not acceptable doses in OAR. CONCLUSIONS: The IMRT technique combined with concurrent temozolamide is well tolerated and offers significant advantages comparing to 3D-CRT. Application of IMRT allows dose reduction at OAR without compromising target coverage

MISCELLANEOUS

P.282. NEURO-ONCOLOGY SCIENTIFIC CLUB AND THE NATIONAL IRANIAN BRAIN TUMOR REGISTRY

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OBJECTIVE: Defining a clinical data gathering system would help categorizing patients' data in a useful, accurate and ordered manner. For brain tumors, apart from North America and UK, and few other European countries, there hardly are comprehensive and organized national registries worldwide. There has always been a room to apply a well designed data registry software which is endorsed by Iranian neuro-oncology experts and is applicable for brain tumor registry purpose nationwide. As an initial important step, during the NOSC meeting (Neuro-Oncology Scientific Club) January 2012 in Tehran, the project entitled the NIBTR (National Iranian Brain Tumor Registry) was launched. There are defined constituted committees to ensure acceptance standards for all patients' data incorporated into NIBTR software. There also are provincial committees as well as a national one to ascertain the accuracy of the inputs. MATERIAL AND METHOD: The registry items were defined based on obtained experts' opinions (interdisciplinary) nationwide and following a thorough search in electronic databases including Medline,Scopus,Cochran Central Register of Controlled

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Trials and ISI for different combinations of "brain tumor" and "registry". These items include the patients' clinical information, the presenting complaints and symptoms,brain tumor related information, imaging data, CSF analysis, pathology reports,surgery data, radiotherapy and chemotherapy protocols and experienced side effects. An additional post mortem section will have the data from those registered patients who die within the 6 month to 1 year follow up period, and have a post-mortem examination. For some cases this may be the only laboratory examination of the brain (thereby substituting for a biopsy as a means of diagnosis). OUTCOME: The expected practical implications of NIBTR would include epidemiologic data gathering, brain tumor patients' treatment and side effects data and follow up results. This leads to elucidation of efficacy and safety of any of the applied treatment strategies in our setting as well as sub-analyses based on recorded and analyzed qualitative and quantitative parameters.

P.284. THE HISTONE DEACETYLASE INHIBITOR, 2-PROPYLPENTANOIC ACID, INCREASES THE CHEMOSENSITIVITY AND RADIOSENSITIVITY OF HUMAN GLIOMA CELL LINES IN VITRO

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The ability of 2-propylpentanoic acid (VPA) to induce the hyperacetylation of histones has led to it being regarded as an agent that might enhance tumor cytotoxicity and radiosensitivity. The present in vitro study investigated the effects of VPA on the sensitivity of human glioma cell lines to chemotherapy and irradiation, and the possible molecular mechanisms involved. Human glioma cell lines, T98-G, and SF295, were treated with temozolomide (TMZ) or irradiation (IR), with or without VPA (1.0 mM). Then, cytotoxicity and clonogenic survival assays were performed. Cell cycle stage, apoptosis and autophagy were also detected using flow cytometry and the MDC incorporation assay. The results showed that VPA alone was mildly cytotoxic in both cell lines with IC50 values of 3.85 $\pm$ 0.58 mM and 2.15 $\pm$ 0.38mM for T98-G and SF295, respectively. The IC50 of TMZ was 0.20 $\pm$ 0.09 mM in T98-G cells, and 0.08 $\pm$ 0.02mM in SF295 cells. When combined with VPA, the IC50 value of TMZ decreased to 0.06 $\pm$ 0.02 mM for T98-G, and 0.05 $\pm$ 0.01 mM for SF295 ($P < 0.05$). The surviving fractions of T98-G and SF295 cells exposed to 2 Gy IR alone were 0.52 and 0.58, respectively. However, when VPA was combined with IR, the SF2 dropped to 0.39 ($P = 0.047$), and 0.49 ($P = 0.049$), respectively. Treatment with VPA plus TMZ or IR also caused a significant decrease in the proportion of cells in the G2 phase and induced the rates of apoptosis and autophagy in T98-G and SF295 cell lines ($P < 0.01$). In conclusion, VPA could enhance the effect of TMZ and IR on glioma cell lines through cell cycle blockage and the promotion of autophagy, and thus could be a potential chemosensitizer and radiosensitizer of gliomas.

P.285. NOT ONLY ANGIOGENESIS BUT ALSO SOME INFLAMMATIONS CAUSE THE AGGRAVATION OF RADIATION NECROSIS IN THE BRAIN - MOLECULAR CONSIDERATION-

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PURPOSE: Radiation necrosis (RN) is a serious problem after intensive radiotherapy. There are 2 major patho-phyisiological hypotheses of RN. One is fragile and leaky angiogenesis caused by overproduction of VEGF and the other is some inflammation. Recently we proved the former hypothesis using human RN specimen and here we analyze the participation of inflammation for patho-physiology of RN using the same specimen. METHODS AND MATERIALS: Eight surgical specimens of symptomatic RN in the brain were retrospectively reviewed by histological and immunohistological analyses using hematoxylin and eosin (H&E) staining, anti-VEGF, HIF-1α, CXCL12, CXCR4, GFAP, CD68 (macrophage marker), IL-1α, IL-6 and TNF-α immunohistochemistry. RESULTS: H&E staining showed marked angiogenesis and cell infiltrations at the peri-necrotic area. The most prominent vasculature in this area was identified as thin-walled leaky angiogenesis, telangiectasis, around which edema (enlargement of interstitial space) was prominent. Immunohistochemistry indicated that HIF-1α was expressed predominantly in the peri-necrotic area. There were 2 major cell phenotypes infiltrated in the peri-necrotic area. One is astrocyte and the other is macrophage. Immunohistochemistry revealed VEGF was produced in reactive astrocytes and not in macrophages. From the standpoint of inflammation, CXCL12, a chemokine was expressed by reactive astrocytes and its receptor CXCR4 was expressed by macrophages. Proinflammatory cytokines, IL-1α were produced by macrophages but no apparent production of TNF-α was observed. CONCLUSIONS: VEGF produced by the reactive astrocytes caused both leaky and fragile angiogenesis and the subsequent peri-lesional edema in RN. On the other hand, reactive astrocytes expressing CXCL12 might draw CXCR4-expressing macrophages at peri-necrotic area. These accumulated macrophages producing proinflammatory cytokines seemed to cause aggravation of RN. Both angiogenesis and inflammation might be caused by the expression of HIF-1 α which is well-known as trans-activator of VEGF and CXCL12-CXCR4 systems. Not only anti-VEGF antibody, bevacizumab but also some antagonists of HIF-1 α or inflammatory cytokines might be effective for the treatments of RN.

P.286. PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY AFTER RITUXIMAB THERAPY IN A PATIENT WITH RELAPSED MANTLE CELL LYMPHOMA IN COMPLETE REMISSION

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INTRODUCTION: Progressive multifocal leukoencephalopathy (PML) is a rare and usually fatal demyelinating disease of the central nervous system (CNS) observed almost exclusively in immunodeficient patients and caused by reactivation of latent JC polyoma virus (JCV) infection. PML has been described in many HIV-negative patients with hematological malignancies after chemotherapy and bone marrow transplantation. In the last years, there have been also reports of PML after rituximab therapy. Diagnosis can be difficult and often a CNS biopsy is required. Current treatment approaches to PML are inadequate.We report here our first verified case of PML in a 55-years old HIV-negative patient with relapsed mantle cell lymphoma (MCL), who was successfully treated for cancer with chemotherapy (ChT), rituximab and autologous hematopoietic stem cell transplantation (AHSCT), but with a fatal outcome of PML. Case report: In 2004, a 48-years old male patient started the treatment of MCL, stage IV.A, with chlorambucil and prednisolone based ChT, which resulted in a complete remission. In 2008, two localized relapses were diagnosed and treated with irradiation of the involved eyelids and neck lymph nodes. In May 2009, the third relapse was treated with rituximab containing regimens (R-CHOP and R-FC). In February 2010, the patient underwent AHSCT and after that started with rituximab consolidation therapy. In total, he received 19 cycles of rituximab. Nine months after the end of rituximab therapy, he developed confusion, gait disturbances, strenght and vision field impairment. Neurologically he was still able to walk, partly desoriented, with left sided hemiparesis and homonymous hemianopsia, construction apraxia and partly disturbed verbal fluency. MRI of the brain disclosed white matter hyperintensity on T2 and FLAIR, hypointensity on T1 and partial contrast enhancement of the right hemisphere and frontal corpus callosum. Blood tests for HIV, CMV, hepatitis B and C were negative. The cerebrospinal fluid (CSF) examination on malignant cells, neurotropic viruses, bacterias and toxoplasmosis was negative. JCV PCR in CSF was not performed at that time, but was positive retrospectively. Progression of lymphoma was excluded and a stereotactically guided brain biopsy was performed. Pathohistological changes were compatible with PML. JCV infection was confirmed with in situ hibridisation. The patient was treated for PML without any effect on neurological symptoms and signs. He continously deteriorated and died in November 2011, 5,5 months after confirmation of PML. CONCLUSION: With this case we wish to emphasize the importance of PML in differential diagnosis in immunocompromised patients with progressive neurological symptoms treated with rituximab and the importance of early detection of JCV in CSF or brain biopsy sample.

P.287. A SIMPLE SCREENING TEST FOR PRE-OPERATIVE MENTAL INCAPACITY IN BRAIN TUMOUR PATIENTS

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Pre-operative neurosurgical assessment of mental capacity is often unstructured and rudimentary. We performed independent assessments of mental capacity and cognition to identify the best simple screening test to identify lack of mental capacity (inability to understand, retain, evaluate and communicate decisions). METHODS: We performed a prospective, blinded, independent assessment of capacity using the McArthur Competence Assessment Tool for Treatment (MaCAT-T) with audiotaped interview (gold-standard) and compared it with a comprehensive, brief

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and reliable bedside instrument for early detection of dementia (the Addenbrookes Cognitive Examination (ACE-R)) and the actual neurosurgical evaluation of capacity in 100 neuro-oncology patients prior to surgery. RESULTS: 100 patients with intracranial tumours were assessed. Age range 17-76; 49 males and 51 females. 8/100 (8%) were so cognitively impaired they were unable to participate in the assessment and were deemed to lack capacity. A further 17/100 (17%) were assessed using the MacCAT-T and ACE-R and were found to lack mental capacity. All 17 exhibited significant cognitive impairment (median ACE-R score 54/100 (IQR 44-73)). The median ACE-R score of the 75/100 patients with mental capacity was 83/100 (IQR 82.5-94). Neurosurgeons felt 11/100 (11%) did not have mental capacity. 18/25 (72%) incapable patients had tumours located in the frontal or temporal lobes and 17/25 (68%) had WHO Grade III or IV tumours. Scores in two subsets of the ACE-R (a score of $<3/7$ for learning an address after 3 attempts combined with a score of $<4/7$ for listing animals in 1 minute) were predictive of mental incapacity (sensitivity 100%, specificity 83% and PPV 66%). CONCLUSIONS: Surgeons are responsible for adequately checking mental capacity pre-operatively. While there are no simple tests to assess mental capacity, a simple screening test can adequately identify patients where more detailed assessment is indicated.

P.288. DOUBLECORTIN-LIKE KINASE: A POTENTIAL THERAPEUTIC TARGET FOR NEUROBLASTOMA

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Doublecortin-like kinase (DCLK) gene encodes microtubule-associated proteins that are crucial for correct proliferation and differentiation of neuroprogenitor cells. Gene expression profiling revealed a high expression of DCLK transcripts in neuroblastomas (NBs). These transcripts are endogenously expressed in neuroblasts but are not found in other cell types. Suppression of DCLK by short interfering RNA (siRNA) disrupted the mitotic spindles in NB cells and gene expression profiling revealed numerous differentially expressed genes indicating apoptosis. Apoptotic cell death of NB cells by DCLK knockdown was further confirmed by several assays. Interestingly, mitochondria were the most affected cell components after DCLK knockdown. In human NBs a highly significant correlation between DCLK expression and genes related with mitochondria activity was detected. In fact, we found that DCLK is crucial for cytochrome c oxidase activity and ATP synthesis in NB cells. Furthermore, DCLK silencing in NB xenograft models in mice resulted in a significant delay in NB tumor growth. Less proliferation and more apoptotic cells were detected in NB tumors with DCLK knockdown than in tumors expressing DCLK. In summary, 1) DCLK is crucial for proliferation and survival of NB cells and 2) in vivo studies showed that NB tumors with DCLK knockdown have a growth delay. Therefore, our results strongly indicate that DCLK is a potential therapeutic target for NB.

P.289. HIGH-DOSE CHEMOTHERAPY WITH AUTOLOGOUS STEM CELL RESCUE FOR RECURRENT MEDULLOBLASTOMA / CNS PNET - A SINGLE CENTER REVIEW

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INTRODUCTION: Despite gradual improvement in the survival rates of newly diagnosed medulloblastoma and other CNS primitive neuroectodermal tumors (PNET), recurrent disease maintains a dismal prognosis. High-dose chemotherapy with autologous stem cell transplant (ASCT) may be beneficial, although controversial. OBJECTIVES AND METHODS: Characterization of a cohort of patients diagnosed with medulloblastoma or CNS PNET, which underwent ASCT after high-dose chemotherapy in recurrence. Data was collected retrospectively from patient records treated at our institution from 1995 - 2011. RESULTS: Seventeen patients underwent ASCT, 14 male patients; median age at diagnosis 12.6 years (2.3-39); 9 children. Diagnosis was medulloblastoma in 14 patients (7 high risk, 7 low risk) and PNET in 3. After diagnosis, all but one patient (2.3 year-old) underwent conventional radiotherapy; adjuvant chemotherapy in 11 patients. At recurrence, 8 patients were treated with surgery, 16 with chemotherapy and 2 with re-irradiation. Disease status at ASCT was: partial response in 4, minimal residual disease in 2, complete response in 10, progressive disease in 1. Eleven patients had high-dose chemotherapy at 1st recurrence, 5 at 2nd recurrence and 1 at 3rd recurrence. Median time to ASCT: 39 months (6-240). Conditioning regimen consisted of carboplatinum + thiotepa + ethoposide in 12 patients, bussulfan + thiotepa in 1, bussulfan + cyclophosphamide in 2, thiotepa + etoposide in 2. Stem cell source was peripheral blood stem cells (PBSC) in 15 patients, autologous bone marrow in 1, both in 1. A median of 2.86×10^6 CD34+ cells/Kg was infused. Engraftment was achieved in all but 2 patients (early death). Median time to platelet engraftment was 17 days (7-101) and 11 days (9-34) to neutrophils. Transplant-related complications were: grade IV mucositis (9), febrile neutropenia (12), bacteremia (7), erythrodermia (1)/Lyell syndrome (1), toxic hepatitis (2), pneumonia (8; 4 needing ventilation); septic shock (4); encephalopathy with seizures (4). Three patients died due to conditioning-related complications. Event-free survival after ASCT: 6 months (13 days - 21 months); median overall survival after ASCT: 10 months (11 days - 83 months); median overall survival after ASCT at 1st relapse: 11.2 months (11 days - 83 months); median overall survival after ASCT of patients treated at 2nd/3rd relapse: 9.4 months (13 days - 37 months). Median overall survival after diagnosis: 51 months (6-240 months). DISCUSSION: High-dose chemotherapy with ASCT had acceptable toxicity, comparing to previous reports with similar regimens (mainly carboplatinum + thiotepa + ethoposide). Despite 35% of patients being treated at the second or third relapse, overall survival after ASCT slightly approached survival in patients treated at first recurrence. These regimens may still be an option even in advanced stages of this disease.

P.290*. TEMOZOLOMIDE FOR RECURRENT INTRACRANIAL EPENDYMOMA OF THE ADULT

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BACKGROUND: Surgery represents the most important treatment modality for intracranial ependymomas. Post-operative radiotherapy is part of standard of treatment in anaplastic ependymoma (WHO gr. III) and can be an option in patients with grade II ependymoma at relapse. There are few data regarding the role of chemotherapy, and platinum-based compounds are considered the best option for recurrent tumors, with response rates between 31% and 67%. Temozolomide (TMZ) has been suggested as an active compound in experimental models of ependymomas, but preliminary clinical reports seem disappointing. Objectives of our study were to investigate the role of TMZ in recurrent intracranial ependymomas of the adult, with particular attention to response rate (RR), progression-free survival (PFS) at 6 and 12 months, overall survival (OS) and tolerability and to evaluate the correlation between MGMT gene promoter methylation status and response to TMZ. PATIENTS AND METHODS: We retrospectively evaluated all adult patients with recurrent intracranial ependymoma treated with TMZ at our Institution from April 1999 till June 2011. The methylation of MGMT promoter was analyzed by PCR. RESULTS: We collected 18 patients (12 M, 6 F) with recurrent gr. II (8/18, 44%) and gr. III (10/18, 56%) intracranial ependymoma: the progression before TMZ was local in 10/18 (56%), local and spinal in 6/18 (33%), spinal alone in 2/18 (11%). Median age at the beginning of treatment was 42 years (range 18 - 61), with a median time from the first surgery of 2 years (range 7 mo-12 yrs). The median KPS was 70 (range 60 - 90). Previous treatments consisted in: gross total resection in 8/18 (44%), partial resection in 9/18 (50%), biopsy in 1/18 (6%), and conventional radiotherapy in 17/18 (94%) patients. Chemotherapeutic agents other than TMZ had already been administered to 6/18 (33%) patients. TMZ was employed at 1st recurrence in 9/18, at 2nd recurrence in 7/18 and at 3rd recurrence in 2/18 patients. A median of 8 cycles (range 1 - 24) was administered. The treatment was well tolerated in 12/18 (67%) patients, whereas hematological toxicity (grade II-III) was observed in 6/18 (33%). Responses were as follows: CR (3/18, 17%), PR (5/18, 28%), with overall RR of 45%; SD (6/18, 33%), PD (4/18, 22%). We observed 3 CR and 1 PR among anaplastic ependymomas compared to 4 PR among gr. II ependymomas. Median PFS was 9 months (range 1 mo - 12 yrs), PFS at 6 and 12 months was 72% and 39% respectively, median OS was 31 months (range 3 mo - 12 yrs). 4/18 (22%) patients are still alive. The evaluation of MGMT expression was feasible in 8/18 (44%): the promoter was methylated in 2 patients, who showed PR and SD respectively, and unmethylated in the remaining 6, who showed 1 PR, 3 SD, 2 PD, respectively. DISCUSSION: TMZ has some activity in recurrent ependymomas, in particular in the anaplastic variant. The probability of response does not seem to be associated with MGMT promoter methylation.

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P.291. BEATSON WOSCC PRE-TREATMENT ASSESSMENT CLINIC FOR GLIOMA PATIENTS: AN UPDATE

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INTRODUCTION: Patients with high grade glioma (HGG) have complex clinical and psychosocial needs and their condition is often unstable. The period between neurosurgical intervention and the start of oncological treatment is a particularly vulnerable time during which patients are attempting to come to terms with their diagnosis while dealing with complex information about impending treatments. With this in mind, a Pre treatment Assessment Clinic (PTAC) was implemented at the Beatson West of Scotland Cancer Centre in September 2010. The aim of the clinic was to prepare treatment and planning schedules, provide additional information and conduct more detailed clinical and psychosocial assessment of patients with high grade glioma (HGG) for whom radical treatment with radiotherapy +/- chemotherapy had been recommended at their first oncology appointment as well as improving recruitment to clinical studies. METHODS: The PTAC was staffed by an experienced Specialist Nurse and Radiographer with a Consultant available if required. Performance status, steroid requirement, current medication, physical and psychosocial symptoms were reviewed and recorded as baseline measurements. The continued suitability of the intended treatment plan was assessed, potential toxicities discussed and informed consent obtained. Numbers of patients screened and entering studies was audited. RESULTS: Over 12 months, 52 patients with HGG considered suitable for radical treatment at first consultation attended the PTAC within 2 weeks. 30% of these were amended to a palliative schedule, usually because of deteriorating performance status. 30 patients were screened (10 for >1 study) and 15 recruited to phase 1 studies.

CONCLUSIONS: The value of this service is apparent in ensuring that:

- accurate assessments of patient needs and performance status are carried out
- treatments slots are utilised appropriately
- quality of life considered
- clinical trials discussed
- informed consent obtained.

In The Beatson West of Scotland Cancer Centre, patients with glioma being considered for treatment are referred to PTAC. We aim to refer patients with HGG within 1 week of diagnosis and referral for low grade glioma within 2-4 weeks of diagnosis. Designated time to screen patients and discuss trial options in detail has promoted optimum screening and participation in complex, phase 1 trials.

P.292. EXTRACRANIAL METASTASES OF EPENDYMOMA - RARE TUMOR WITH POOR PROGNOSIS

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INTRODUCTION: Ependymoma is a rare tumor, represents less than 10% of CNS tumors and 25% of spinal cord tumors. Incidence is similar in men and women. There are 4 subtypes: myxopapillary ependymoma (WHO GI), Subependymoma (WHO GI), Ependymoma (WHO GII) and Anaplasic Ependymoma (WHO GIII). The standard treatment is complete resection followed by adjuvant Radiotherapy. Recurrence may be local, a distance or both. The importance of case report is due to its low incidence, the peculiarity of metastases pleural, peritoneal, and meningeal and little progression-free interval. CASE REPORT: Female 16 years old. Personal History without interest. November 2010 began with headache and vomiting that do not improvement to treatment and subsequently also accompanied by diplopia. CT: Tumor frontal skull right parasagittal cystic tumor with intense peripheral enhancement with contrast and presence of nodular and heterogeneous solid pole, compatible with primary brain tumor. RMI: Focal intracranial lesion right frontal parasagital, 6x4.5x4.8 cm, cyst. Polo solid heterogeneous in its medial portion in contrast and displaced midline contralaterally. It intervenes by frontal craniotomy with excision of tumor. Pathology: Anaplasic ependymoma GII. In December 2010 ependymoma recurrence. It reoperated and Radiation therapy between January and March 2011 at doses 60/2 Gy. In April 2011 (4 months after diagnosis) begins with dyspnea. In imaging is demonstrated left pleural effusion and pleural metastatic implants. It performed various thoracentesis wich were negative result. The patient died 15 days because of respiratory failure. Necropsy is performed which concludes: anaplasic ependymoma recurrence frontal lobe. Massive pleural implants level of serous peritoneal, subcutaneous tissue and meninges shell. (See pictures). DISCUSSION: There are very few cases described in the literature of extracranial metastases of anaplasic ependymoma. Are estimated to occur in 0.4 to 2% of cases, but amounts to 25% in cases where the autopsy is performed. The mechanism appears to be occurring hematogenous dissemination, although it is unclear. More locations described are: lung, pleural and lymph nodes. Usually appear to 5 years of initial diagnosis. Described some factors that may precipitate the occurrence of extracranial metastases ependymoma: early onset of disease, number of local surgery, prolonged survival after diagnosis and local recurrence at the time of diagnosis of distant metastases. CONCLUSION: 1. Ependymoma is rare in adolescents and poor prognosis. 2. The treatment is the most radical surgery and Radiotherapy 3D. 3. We must take into account the possibility of extracranial metastases for a proper diagnosis. 4. It is advisable to performing necropsy on patients with rare CNS tumors.

P.293. OSMOTIC BLOOD-BRAIN BARRIER DISRUPTION AS DELIVERY STRATEGY TO BYPASS THE BLOOD-TUMOR BARRIER

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Glioblastoma multiforme (GBM) is the most frequent primary malignant brain tumor. Despite decades of research, the median survival of GBM patients remains limited (12 to 14.6 months) and responses obtained with standard care are invariably transitory. This poor prognosis can be attributed to three factors: i) the propensity of glioma cells to invade brain parenchyma, ii) the chemo- and radio-resistance of the tumor cells and iii) the presence of the blood-brain barrier (BBB) that limits drug delivery. Recent studies have exposed that the blood-tumor barrier (BTB) is also involved in drug delivery limitations. Many drug delivery strategies have been developed to bypass the BBB. One of them, the osmotic blood-brain barrier disruption (BBBD) was even shown to increase the median survival in GBM patients (32.2 months). In this study we detail the impact of the BTB and the BBB hampering in drug delivery as well as the impact of BBBD in improving delivery parameters. To achieve these goals, we performed dynamic contrast enhanced-MRI (DCE-MRI) studies on normal and glioma-bearing rats. The animals were imaged with a Varian 7T small animal MRI scanner using T1-weighted dynamic acquisitions. Brain delivery was monitored in real-time using two distinct contrast agents (CA), Magnevist (0.9 kDa) and Gadomer (17 kDa) to mimic the accumulation of antineoplastic agents harbouring different molecular weights. As expected, the BTB shows some degree of permeability. However, the exposure to the tumor was three-fold higher for Magnevist (5.94 mM*min) than for Gadomer (1.58 mM*min). Consequently, BTB permeability appears to be drug-dependant. The BBBD procedure increased by two-fold the CAs signals in the tumor compared to controls, for both molecules. Yet, tumor exposure to Magnevist (12.05 mM*min) was still three-fold higher than for Gadomer (4.76 mM*min). Thereby, the BBBD significantly improves drug delivery across the BTB in a drug-dependant manner. More so, the BBBD procedure significantly enhanced whole brain exposure to the CAs when administrated 3 minutes post-BBBD compared to control groups. Next, We then studied the BBBD therapeutic window. The time course to closure for Magnevist was longer than 30 minutes, while it was relatively short for Gadomer, as the BBB appeared to recover its integrity in 30 minutes. Interestingly, Gadomer was still detectable twelve hours after the BBBD procedure while Magnevist was washed-out in approximately 4 hours. Theses results demonstrate that the BTB represents a major obstacle to drug delivery and that the BBBD significantly enhances tumor and brain exposure to small and large molecules. Our study also reveals that the BBBD process appears to be drug-dependant. Consequently, chemotherapy infusion protocols following BBBD should be optimized according to the properties of the drug administrated.

P.294. IRRADIATION OF PITUITARY MACROADENOMA: ASSESSMENT OF ADJUVANT OR RADICAL TREATMENT

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INTRODUCTION: Pituitary adenomas represent 10 to 20% of all primary brain tumors and, based on autopsy series and magnetic resonance (MRI) surveys, it is estimated that 10-20% of the normal adult population harbors pituitary abnormalities. Treatment is indicated to lesions hormonally active and/or causing mass effect by increasing size. Surgery is the treatment of choice whereas radiation therapy represents a treatment option for residual/recurrent tumors or for poor surgical candidates. OBJECTIVE: The authors report the outcome of patients (pts) with Pituitary Macroadenomas (MA), after radical or adjuvant external radiotherapy (RT). METHODS: Twenty one pts, with MA (non-secretor - 14 pts; secretor - 7pts), undergone external RT (stereotactic - 11pts; conformal - 10pts) as part of their treatment management, from 2004 to March 2011; 13 females and 8 males with a mean age of 50 years (range 24-73). Except for 1 pt, with irressecable MA (submitted to RT radical), all had subtotal surgical approaches (mean of 2 procedures), followed by RT, started in a mean

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time of 16.4 months (range 2-106). All pts had computed tomography based treatment planning with MRI. The fractionation regimen was conventional with 1.8 or 2 Gy per day, 5days per week, to a mean total dose of 52.8 Gy (range 48.6-54). No treatment interruptions were documented. Periodic evaluation included disease specific history, laboratorial analysis, ophthalmological examination and MRI. RESULTS: With a mean follow-up of 34.5 months (range 3-84), 1 pt had tumor progression, documented by MRI, 24 months after RT, and undergone a new surgery. Treatment morbility was limited to Grade I-II acute side effects (Common Terminology Criteria for Adverse Events version 4.03) in 2 pts (9.5%). Endocrine and visual functions were stable in all pts. No late side effects were seen. The 5-year actuarial progression-free survival was 90%. CONCLUSIONS: RT, after subtotal surgical resection or as radical treatment, is a feasible and effective therapeutic option, without associated early or late side effects. This retrospective analysis supports literature findings, however, a longer follow-up and an increase number of patients are needed in order to improve the power of our data.

P.295. POTENTIAL FOR RECURRENCE AND EXTRANEURAL METASTASIS OF MENINGEAL HEMANGIOPERICITOMA (HPC): A RETROSPECTIVE SERIES IN A SINGLE INSTITUTION

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HPC is a rare malignant tumour with a high proclivity toward recurrence and metastasis. The purpose of this study was to analyse retrospectively a series of eighteen patients with HPC treated between January 1992 and Oct 2011 with respect to clinical presentation, treatment results and long-term follow-up outcomes. Survival rate and progression free survival (PFS) were analyzed by Kaplan-Meier method, with the use of two-sided log-rank test statistics. Twelve were females with a median age of 44.5 years (21-62). In 17 patients the tumor was intracranial, in the other one was in the spinal cord. Median follow-up was 77.5 months (6 -316). Eight underwent gross total resection (GTR) and 2 of them received adjuvant radiotherapy. Ten had subtotal resection (STR) and 2 of them received RT. Three out of 6 with GTR without RT relapsed. All patients with STR suffered local progression (2 after RT). Six developed systemic metastases after reiterate surgical resection (more than 3); four of them are alive after further treatment at 1, 11, 18 and 28 months. The median PFS was 43.5 months (4-264), with 2 and 5-year PFS rates of 88% and 27% respectively. The 2, 5 and 10-year survival rates was 100, 93 and 82% respectively. All patients with GTR are alive (median follow-up: 62.5 months, range 32-127) and 3 out of 10 patients with STR died (median follow-up: 81.5 months, range 4-314). When safe and feasible, GTR should be pursued as an initial surgical strategy to maximize overall survival. Adjuvant RT may show promise for preventing tumor progression in GTR patients. Long term survival could be achieved in metastatic disease. The lack of a standard of care for HPC patients makes it especially important to do a complete workup, especially among patients suffering from local recurrent HPC.

P.296*. HEMATOTOXICTY OF ANTICONVULSANTS DURING CONCOMITANT RADIOCHEMOTHERAPY IN PATIENTS WITH GLIOBLASTOMA. PRELIMINARY RESULTS OF AN ONGOING TRIAL

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INTRODUCTION: Interactions of chemotherapeutic agents and antiepileptic drugs (AED) are increasingly becoming of interest with respect to hematotoxicity and their possible influence on anticancer treatment. The co-administration of AED and chemotherapeutic agents in patients with glioblastoma multiforme (GBM) is common. The purpose of this study was to evaluate the possible effects of anticonvulsants on hematotoxicity during concomitant radiochemotherapy. METHODS: From a neurooncological computerized database, 53 consecutive patients with GBM were included in this study. 34 controls with no AEDs, 11 patients receiving levetiracetam (LEV) and 8 patients with valproic acid (VAL) were analyzed. Laboratory follow up examinations were performed within 14, 30, and 45 days after initiation of concomitant radiochemotherapy and within 4 to 8 weeks (final follow up) after completion of concomitant phase. Cytopenia was graded according to the NCI-CTC criteria for hematotoxicity. For statistical calculation, intergroup differences and repeated measures analysis regarding hematotoxicity were calculated by Mann-Whitney-U test. RESULTS: Gender ratio and age distribution in all three groups was comparable to epidemiological data. Lymphocytes were significantly lowered in all groups (Non-AEDs and LEV: $p < 0.01$; VAL: $p = 0.01$) during all consecutive laboratory examinations. In Non-AEDs and VAL, a median lymphopenia grade 1 was observed after 30, 45 days and final follow up. LEV in contrast showed a lymphopenia grade 2 in the last two follow up examinations. Thrombocytes also were significantly reduced over time in all groups (Non-AEDs: $p < 0.01$, VAL: $p = 0.03$, LEV: $p = 0.06$), but most pronounced in the LEV group. A significant decrease in neutrophils was also observed over time (Non-AEDs: $p < 0.01$, LEV: $p = 0.03$). Erythrocyte count showed no significant change during entire follow up in all groups. Regarding intergroup analysis, no difference was observed between changes in lymphocytes and neutrophils during follow up. Comparing Non-AEDs and LEV, thrombocytes were significantly decreased in the LEV group. DISCUSSION: Our results indicate, that VAL as well as LEV influence the hematotoxicity of temozolomide during concomitant radiochemotherapy in GBM. In the literature there is some evidence that VAL acid might be responsible for increasing hematotoxicity, but also provides some evidence for antitumor activity. Hematotoxicity from LEV during chemotherapy has been reported in single case studies. This is the first case control study for patients with GBM and symptomatic seizures, showing a hematotoxic effect of LEV as compared to patients without anticonvulsants. Whether there is an effect on outcome of GBM patients receiving LEV or VPS, as compared to patients without anticonvulsants will be evaluated within in this ongoing trial.

P.297. GAMMA KNIFE RADIOSURGERY IN THE TREATMENT OF HEMANGIOBLASTOMAS IN PATIENTS WITH VON HIPPEL-LINDAÚS DISEASE (VHL)

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INTRODUCTION: VHL is a familial neoplastic rare disease, with a prevalence of 1/45.000 people, related with defects in the VHL oncosupressor gene. In the central nervous system, 80% of patients presents with hemangioblastomas (HGB) in the cerebellum, brainstem and spinal cord, and exceptionally in the supratentorial compartment. Tipically they are multiple, with an estimation of appearance of a new tumor every 2.5-3 years. The successive surgeries performed in these patients are a cause of morbidity and even mortality, and in this setting Radiosurgery has been proposed as an alternative treatment. But, the potential oncogenic effect of Radiation Therapy, in patients with a genetic conditions predisposing to de development of tumors must be kept in mind. OBJECTIVES: The analysis of our results and those from the literature in the treatment of HGB, specifically in VHL patients. PATIENTS: Between 1994 and 2011, 19 treatment in 15 patients have been performed, for a total of 41 HGB. Two patients were treated in more than one occasion. Seven of these patients had a known diagnosis of VHL. The mean age was 37.4, and the gender ratio was 1/1. No patient had received previous Radiotherapy, and 13 had previous surgeries. The mean volume treated was 4.4 cm^3 with a mean marginal dose of 13.9 Gy and a mean follow up of 5 years. RESULTS: The volumetric control was obtained in 72% of the lesions.Clinically 12 patiens remain stable. In all VHL patients new lesions appeared. One patient suffered from edema that required lengthy steroid treatment, and a delayed neuropathy appeared in another. No malignization of a previous lesion has been detected. CONCLUSIONS: From our results and those from the scarce published series we may conclude that best results are obtained with small, solid lesions and doses higher than 15 Gy. In VHL patients a cautious evaluation of the dose received by the healthy surrounding tissues must be performed. In these patients Radiosurgery must be reserved for those cases in which surgery is not possible in experienced hands.

P.298. MOBILE CLINICAL DECISION SUPPORT SYSTEMS FOR IMPLEMENTATION OF NEUROONCOLOGICAL GUIDELINES

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BACKGROUND: Bringing evidence to practice is a key issue in modern medicine. A review of physician guideline adherence shows that volume of information and time needed to stay informed are recurrent barriers. Clinical decision support systems (CDSS) have repeatedly been suggested as a useful tool for improving guideline adherence and mobilizing evidence based knowledge into daily clinical practice. Handheld computers provide mobile decision support that may facilitate this process. METHODS: An existing application for iPhone, iPad and Android (called "NeuroMind") has been improved to support interactive CDSS. It has been tested by automating algorithms published in peer-reviewed literature. Lately a Dutch national guideline on the diagnosis and treatment of brain metastases has been converted to an interactive mobile CDSS too. Besides intracranial disease,

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the app also offers support for spinal neoplastic disease. RESULTS: Although no formal user evaluation has been performed to date, informal user evaluations provided positive feedback regarding usability of the user interface. The interactive features and "personalized" approach are regarded as the strongest features of the application. The lack of integration in the hospital's electronic health records was the main criticism. CONCLUSION: Mobile CDSS can help to facilitate information access and guideline adherence. Development of such interactive applications is feasible nowadays, and the results for a neurooncological implementation will be presented.

P.299. PERICHIASMATIC HEMANGIOBLASTOMAS IN VON HIPPEL-LIDAU DISEASE - EXPERIENCE IN A PERSONAL SERIES

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OBJECT: Hemangioblastomas are benign tumors of the Central Nervous System composed of neoplastic stromal cells and vessels, that can occur sporadically or in the context of von Hippel-Lindau disease (VHL). They are most frequently located in retina, cerebellum, spinal cord and brainstem in VHL patients. Supratentorial location is seldom seen, but isolated reports suggest pituitary stalk as the most frequent site within the supratentorial compartment. To better understand the incidence, clinical effects and management of hemangioblastomas of the perichiasmatic region, we analyze our experience in VHL patients. MATERIAL AND METHODS: A retrospective survey of clinical, imaging and hormone levels has been performed on patients with hemangioblastomas located in the perichiasmatic area, diagnosed by MRI, in a series of 92 VHL patients, evaluated and treated in a Neurosurgery department with special dedication to Familial Neuro-oncology patients. A review of published perichiasmatic hemangioblastomas has been performed, comparing the results in order to get a common pattern of behavior and management. RESULTS: Ninety two patients have been included in the study. In four patients (4.35%) a supratentorial hemangioblastoma has been diagnosed: one patient with perichiasmatic and temporal tumors, one perichiasmatic hemangioblastoma in another patient, one parietal tumor in the third and a pineal hemangioblastoma in the fourth (five supratentorial tumors in all). In both cases of "perichiasmatic" tumors, MRI showed a solid enhancing tumor without associated cyst above the pituitary stalk (one in the lamina terminalis). In both patients, basal plasmatic hormone profiles and visual fields were normal. Both patients remained asymptomatic and the image stable with no treatment at follow-up of 6 and 2 years respectively. In the literature review, only a series with eight cases and five "case reports" have been found. Cases from the series were all asymptomatic and stable at follow-up, and they were diagnosed in MRI studies performed following sequential protocol for VHL patients, whereas cases referred as "case reports" were diagnosed because they were symptomatic and required surgical treatment; this different behavior may be related to reference bias. CONCLUSIONS: The perichiasmatic region is the most common site for the location of supratentorial hemangioblastomas in VHL patients, although the accuracy of MRI studies shows that not all those tumors are located just in the pituitary stalk, as it has been stated up to now. Although symptomatic isolated cases have been diagnosed and reported, perichiasmatic hemangioblastomas often remain asymptomatic and do not require treatment, but should be managed with image and clinical observation. Surgery can be reserved for symptomatic and/or growing tumor cases.

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