ORAL PRESENTATIONS

NEURO-IMAGING I

O.01. INFLUENCE OF P-GLYCOPROTEIN EXPRESSION ON $^{99mTc}$-TROTOFOSMIN UPTAKE IN GLIOMAS

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

MATERIALS AND METHODS: Eighteen patients (10 males, 8 females, mean age 57.3 years) with histologically confirmed glioma were included in the study. There were 13 glioblastoma multiforme cases, 2 anaplastic astrocytomas, 2 anaplastic oligodendrogliomas, and 1 low grade astrocytoma. Brain SPECT by $^{99mTc}$-TF was performed within a week prior to surgical excision and the expression of P-gp was assessed by immunohistochemistry. Radiotracer accumulation was assessed by a semiquantitative method of image analysis, calculating the lesion-to-normal tissue (L/N) uptake ratio. RESULTS: The tracer uptake ranged from faint to profound (mean L/N = 82.2, range 1.8–20). The P-gp expression ranged from 0% to 45%. Using Spearman’s rho analysis we found no correlation between tracer uptake (L/N) and P-gp expression (P = .21, r = .538). CONCLUSION: The present data suggest that $^{99mTc}$-TF uptake is not influenced by P-gp expression in gliomas. Thus, $^{99mTc}$-TF constitute a suitable radiotracer for gliomas imaging.

O.02. PERFUSION MR IN DIFFERENTIATING BETWEEN TUMOR-PROGRESSION AND PSUEUDO-PROGRESSION IN RECURRENT GLOBLASTOMA MULTIFORME

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OBJECTIVES: The aim of this study was to evaluate perfusion magnetic resonance imaging (pMRI) for differentiation of tumor progression (PD) from pseudo-progression (Ps-PD) in patients with recurrent glioblastoma multiforme (GBM) following chemoradiation. BACKGROUND: The appearance of Ps-PD on brain MR following initial chemoradiotherapy is difficult to distinguish from true PD. We examined whether the technique of pMRI allows proper distinction between PD and Ps-PD in patients with recurrent GBM. METHODS: All files of patients with GBM with pMRI and 1 MR scan including pMRI 3 months later. Patients had recurrent GBM, and adjuvant temozolomide (TMZ). At first recurrence, 80 patients were treated with surgery followed by radiotherapy (RT) and concurrent and adjuvant temozolomide (TMZ). At first recurrence, 80 patients were treated with single agent, bevacizumab. At time of progression, 57 patients were treated with bevacizumab and a cytotoxic chemotherapy, cytotoxic chemotherapy alone, or on an investigational trial. Magnetic resonance imaging (MRI) were analyzed at four time points in each patient: at presentation, at first, second, and third recurrence. Four patterns of radiographic disease were assessed, local (unifocal disease), distant (second lesion noncontiguous with primary lesion), multifocal (>2 lesions including leptomeningeal dissemination), and diffuse. RESULTS: At presentation, 87.5% of glioblastoma were local, 6.25% diffuse, 3.75% multifocal, and 2.5% diffuse. At first recurrence following progression on RT/TMZ and before initiation of bevacizumab, 80% were local, 7.5% distant, 6.25% multifocal (including 1 with CSF dissemination), and 6.25% diffuse. At second recurrence following progression on bevacizumab, 71.25% were local, 8.75% distant, 8.75% multifocal (of 7 with CSF dissemination), and 11.25% were diffuse. At third recurrence (57 patients evaluable), 71.25% were local, 7.0% distant, 7.0% multifocal, and 14.0% were diffuse. Survival following progression on bevacizumab did not differ by pattern of radiographic recurrence. CONCLUSION: A majority of adult patients with GBM at diagnosis manifest MRI-defined local disease and maintain this pattern notwithstanding multiple recurrences and treatment with bevacizumab.

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

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BACKGROUND: Response assessment in malignant glioma following antiangiogenic treatment is challenging for conventional MR imaging (MRI). Despite decreased contrast-enhancement, non-enhancing parts of the tumor may continue to grow. In this retrospective study, we analyzed patients with recurrent malignant glioma during Bevacizumab/Irinotecan therapy using ADC map image analysis from diffusion-weighted MRI to yield ultrastructural information on cellular density and properties of the extracellular matrix in relation to the progression-free survival. METHODS: Fifteen patients treated with Bevacizumab/Irinotecan for recurrent malignant glioma were investigated by MRI every 2–3 months until tumor progression. Applying image segmentation, volumes of contrast-enhanced lesions on T1 and hyperintense nonenhancing T2 lesions were calculated. T2 hyperintense lesions were defined as regions of interest (ROIs) and registered to the corresponding ADC maps (T2-ADC). Histograms and cumulative histograms of the T2-ADC ROIs were calculated to quantify the apparent gray scale value distribution and were compared with progression-free survival. Software programs were used to perform segmentation (ITK-Snap), calculation of T2-ADC histograms (Imag), and statistical figures (SPSS). RESULTS: At 3-month follow-up, the overall mean contrast-enhanced T1 volume (in cm3) decreased significantly from 266 ± 197 (7.94–7.14, p = .021) to 54 ± 25 (4.5 ± 29.4, p = .021). According to Macdonald criteria, 12 patients showed response and 3 patients progressed. During the same period of time, the mean T2 volume (in cm3) was significantly reduced in 8 cases (P = .005) from 127.32 ± 59.01 to 85.61 ± 42.12 and increased in 7 cases (p = .080) from 140.93 ± 50.91 to 203.22 ± 126.52. T2-ADC cumulative histograms showed differences in terms of gradient and kurtosis. In 8 cases an increasing gradient and high kurtosis represented an increased amount of low ADC grey scale values that can be interpreted as an augmentation of cellular density of the tumor. These patients showed a lower chance of progression-free survival compared with patients (n = 6) with a decreasing slope and low kurtosis of the T2-ADC cumulative histograms. CONCLUSION: Changes in grey scale distribution in ADC cumulative histograms in patients with malignant recurrent glioma may be predictive for antiangiogenic treatment response.

O.04. RADIOGRAPHIC PATTERNS OF RELAPSE IN GLOBLASTOMA

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BACKGROUND: Glioblastoma (GBM) is defined pathologically as an infiltrative glioma, and salvage therapy with bevacizumab is believed to increase the incidence of diffuse and distant invasion as assessed radiographically. PATIENTS AND METHODS: 80 adult patients with glioblastoma were treated with surgery followed by radiotherapy (RT) and concurrent and adjuvant temozolomide (TMZ). At first recurrence, 80 patients were treated with single agent, bevacizumab. At time of progression, 57 patients were treated with bevacizumab and a cytotoxic chemotherapy, cytotoxic chemotherapy alone, or on an investigational trial. Magnetic resonance imaging (MRI) were analyzed at four time points in each patient: at presentation, at first, second, and third recurrence. Four patterns of radiographic disease were assessed, local (unifocal disease), distant (second lesion noncontiguous with primary lesion), multifocal (>2 lesions including leptomeningeal dissemination), and diffuse. RESULTS: At presentation, 87.5% of glioblastoma were local, 6.25% diffuse, 3.75% multifocal, and 2.5% diffuse. At first recurrence following progression on RT/TMZ and before initiation of bevacizumab, 80% were local, 7.5% distant, 6.25% multifocal (including 1 with CSF dissemination), and 6.25% diffuse. At second recurrence following progression on bevacizumab, 71.25% were local, 8.75% distant, 8.75% multifocal (of 7 with CSF dissemination), and 11.25% were diffuse. At third recurrence (57 patients evaluable), 71.25% were local, 7.0% distant, 7.0% multifocal, and 14.0% were diffuse. Survival following progression on bevacizumab did not differ by pattern of radiographic recurrence. CONCLUSION: A majority of adult patients with GBM at diagnosis manifest MRI-defined local disease and maintain this pattern notwithstanding multiple recurrences and treatment with bevacizumab.
DTI-fiber tracking (DTI-FT) allows the reconstruction of subcortical tracts and their relationship with tumors. This work assesses the ability of preoperative DTI-FT to predict the extent of resection achievable during surgery of gliomas performed with intraoperative brain mapping. A total of 220 patients with gliomas (mostly low grade) were included. In all patients, the corticospinal tract (CST), the internal fronto-occipital (IFO), and superior longitudinal (SLF) fasciculi were reconstructed by DTI-FT. The relationship of each of the tracts (CST, IFO, and SLF) with the tumor mass was scored by two independent observers as being unchanged, dislocated, or infiltrated. Intraoperative protocol included intraoperative language and motor mapping and monitoring (EEG, ECoG, EMG, and MEP). DTI-FT images were loaded into the neuronavigation system and available during surgery. Surgery was carried out according to functional boundaries. For each patient, preoperative and postoperative MR images and DTI-FT were loaded into the neuronavigation software and image fusion was used to evaluate the extent of resection as well as the correspondence between the resection boundaries and the preoperative DTI-FT. A correlation between the preoperative score of each tract and the extent of resection (scored on FLAIR volumetric images) was then investigated. Most of the tracts were inside and infiltrated by the tumor (80%); 40% of the tumor showed more than one tract infiltration. Tract infiltration depended on tumor location and volume, being more frequently observed in Rolandic and large tumors. No tract infiltration was documented by DTI-FT, the extent of resection was total in all the cases. When one tract was infiltrated, extent of resection was total in 70% of the cases on the average, which decreased to 45% and to 33% when 2 or 3 tracts were involved, respectively. The involvement of CST and IFO was more frequently associated with a reduced chance of resection. Preoperative evaluation in DTI-FT of the level of subcortical tracts (mainly CST and IFO) is an important tool for the chance of performing a total resection. When CST and IFO are infiltrated by the tumor, a total removal is rarely possible; when were outside, an extensive resection is feasible. Preoperative DTI-FT identifies those patients who will mostly benefit from surgery.

O.06. USEFULNESS OF MET-PET, FLT-PET, AND FMISO-PET FOR SURGICAL TREATMENT OF GLIOMAS
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OBJECTIVE: L-[Methyl-11C]methionine (MET) positron emission tomography (PET), [18F]-fluoro-3-deoxy-3-fluorothymidine (FLT) PET, and [18F]-fluoromisonidazole (FMISO) are sensitive modalities for visualizing proliferative or hypoxic tumor tissue. The objectives of the present study were to compare the relationships between uptake of MET, FLT, or FMISO and the histopathological grading in gliomas. METHODS: We examined 51 patients (22 males, 29 females; mean age: 48.7 years; range: 2–89 years; 10 diffuse astrocytomas, 1 oligodendroglioma, 17 low-grade gliomas, 5 anaplastic astrocytomas, 1 anaplastic oligodendroglioma, 1 anaplastic ependymoma, and 22 glioblastomas), using MET-PET studies preoperatively. Moreover, 35 patients (17 males, 18 females; mean age: 51.4 years; range: 22–81 years; 6 diffuse astrocytomas, 1 oligodendroglioma, 5 anaplastic astrocytomas, 1 anaplastic oligodendroglioma, 1 anaplastic ependymoma, and 21 glioblastomas) were examined with FLT-PET. Finally, 10 patients (6 males, 4 females; mean age: 55.8 years; range: 30–72 years; 1 diffuse astrocytomas, 2 anaplastic astrocytomas, 7 glioblastomas) were examined with FMISO-PET. MET, FLT, and FMISO uptakes were assessed by standardized uptake value of the tumor showing the maximum uptake (SUVmax), and the ratio of tumor tissue to normal gray matter (T/N ratio). The tumor activity and degree of malignancy were evaluated using Ki-67 index. The correlations between SUVmax and Ki-67 index were determined by linear regression analysis. RESULTS: All glioblastomas showed tumor uptake of MET, FLT, and FMISO. The difference in MET T/N ratio was statistically significant between grade II and IV gliomas, but not significant between grade II and III gliomas. The difference in FLT T/N ratio was statistically significant between grades III and IV gliomas, but not significant between grades II and III gliomas. The difference in FMISO T/N ratio was statistically significant between grades III and IV gliomas. FLT SUVmax in the tumor had a stronger correlation with Ki-67 index than MET SUVmax. CONCLUSIONS: PET studies using MET, FLT, and FMISO are useful for preoperative diagnosis in gliomas. FLT–PET seems to be superior to MET–PET in assessment of the proliferation activity on gliomas of different grades. FMISO–PET is useful for non-invasive assessment of hypoxia in malignant gliomas. Advances in molecular imaging such as PET imaging techniques will facilitate more safe and solid management and therapy for the patients with malignant gliomas.

O.07. MGMT PROMOTER METHYLATION STATUS AND EXPRESSION OF DNA MISMATCH REPAIR GENES IN PAIRED PRIMARY AND RECURRENT GLOBLASTOMA: A RETROSPECTIVE STUDY OF THE GERMAN GliOMA NETWORK
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INTRODUCTION: Hypermethylation of the MGMT promoter is strongly associated with longer progression-free and overall survival in glioblastoma (GBM) patients treated with radiotherapy and concomitant and adjuvant chemotherapy. We have addressed the question whether GBM relapses are associated with changes in the MGMT promoter methylation status or altered expression of the DNA mismatch repair genes MLH1, MSH2, MSH6, or/and PMS2. METHODS: MGMT promoter methylation status was determined in primary tumors, 28 recurrent primary tumors, using nonquantitative methylation-specific PCR (MSP). The vital tumor cell content of each primary and recurrent tumor specimen was histologically determined. Quantitative promoter methylation analyses using DNA pyrosequencing (MGMT, MLH1, MSH2, MSH6, and PMS2) for DNA mismatch repair genes MLH1, MSH2, MSH6, and PMS2 proteins were analyzed semiquantitatively by immunohistochemistry (IHC) in 43 patients. RESULTS: MSP revealed MGMT promoter hypermethylation in 27 patients, borderine methylation in 3 patients, and no methylation in 50 patients at diagnosis. In 73 of the 80 patients, the MGMT promoter status of the primary tumor was retained at recurrence. In 6 patients, loss or re methylation of MGMT promoter methylation was detected in the recurrent tumor; however, in 3 patients, this finding was explained by low tumor cell contents in the recurrent tumor specimens. In 1 patient, a change from MGMT borderline methylation (8% methylated alleles) to hypermethylation (50% methylated alleles) was detected. None of the investigated primary and recurrent glioblastomas showed MLH1, MSH2, MSH6, or PMS2 promoter hyperhypermethylation. However, immunohistochemical expression scores for MLH1, MSH2, MSH6, and PMS2 proteins were frequently reduced in the recurrent tumor when compared with the corresponding primary tumor.
CONCLUSION: The MGMT promoter methylation status does not change from the primary to the recurrent tumor in the vast majority of GBM patients. Accordingly, changes in the MGMT promoter methylation status are unlikely to account for acquired resistance to temozolomide. Our results further suggest that GBM recurrences often demonstrate lower MLH1, MSH2, MSH6, and/or PMS2 immunoreactivity scores. However, MLH1, MSH2, MSH6, and PMS2 promoter hypermethylation does not appear to account for these changes in protein levels and its effects are not linked to GBM recurrence. Accordingly, the changes in the MGMT promoter methylation status are unlikely to account for acquired resistance to temozolomide.
tumor resections (25 patients) and stereotactic biopsies (39 patients) were used for subsequent analyses. MGMT promoter methylation was determined by methylation-specific PCR (MSP). MGMT mRNA expression was analyzed by real-time qPCR and normalized against adequate housekeeping genes. Primary endpoint was progression-free survival (PFS). Secondary endpoints were overall survival (OS) and treatment response (TR). RESULTS: Histopathological diagnosis revealed 54 glioblastoma multiforme and 10 anaplastic astrocytomas. Thirty-two tumors were methylated and 32 tumors exhibited a low MGMT transcriptional activity (cut-off value: 0.45), respectively. Low MGMT mRNA expression turned out to be a strong predictive factor for PFS, OS, and favorable TR in univariate and multivariate models (P < .0001); even though the degree of MGMT mRNA expression strongly correlated with the methylation status (P < .0001), discordant findings were seen in 30% of the patients: Patients with a methylated tumor and high MGMT mRNA expression (15%) did significantly worse than those with low transcriptional activity (P < .05). Conversely, patients with a methylated tumor and low MGMT mRNA expression (15% of the unmethylated tumors) did better than their counterparts. CONCLUSION: Determination of MGMT mRNA expression is a powerful method for predictive evaluation of malignant and nonmalignant tumors, nonneoplastic tissues with low MGMT mRNA expression (15% of the unmethylated tumors) did better than their counterparts. A substantial rate of discordant findings elucidates the fact that treatment decision in favor of chemotherapy with alkylating agents should not be based on the MGMT methylation status alone.

**O.09. UPDATED RESPONSE ASSESSMENT CRITERIA FOR HIGH-GRADE GLIOMAS (HGG): REPORT FROM THE RESPONSE ASSESSMENT IN NEURO-Oncology (RANO) Working Group**

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**Abstract:** Accurate determination of response and progression is crucial to evaluate new brain tumor treatments and care for patients. Macdonald’s criteria (Macdonald et al. Clin Oncol. 1990; 8:1277–80), based on measuring cross-sectional enhancing tumor area, taking into account changes in steroid dose and neurological status, have been widely used. Limitations include difficulty in measuring tumors with complex shapes or indistinct borders, nonneoplastic tissues that produce imaging changes, reaction to local therapies, posttreatment changes that may mimic tumor, and lack of applicability to nonenhancing tumors. Anti-angiogenic therapies, which reduce MRI enhancement by restoring the blood-brain barrier, while nonenhancing tumor may enlarge, highlight the difficulty of assessing novel treatments. The RECIST criteria use unidimensional tumor measurements, do not consider steroids or neurological status, and have the limitations of Macdonald’s criteria. The RANO group is an ongoing international multidisciplinary consensus building effort to develop new response criteria. The now published RANO criteria for HGG measure cross-sectional enhancing and nonenhancing tumor area, and account for the changes in steroid dose and neurological status (Wen et al. J Clin Oncol. 2010; 28(36):4399–4409). Within the first 12 weeks of completing chemo-radiation, progression requires either new tumor outside the high-dose radiotherapy field or biopsy-proven tumor, to avoid “pseudoprogression.” T2/FLAIR images receive more emphasis, particularly in trials on anti-angiogenic agents. Hindgut may allow a more accurate determination of progression and is now a formally described part of the outcome assessment procedure. Increase of steroids alone is still not perceived as sufficient evidence of progression.

**O.10. A PROSPECTIVE, RANDOMIZED, OPEN LABEL, PHASE III CLINICAL TRIAL OF NOV0TTF-100A VS BEST STANDARD OF CARE CHEMOTHERAPY IN PATIENTS WITH RECURRENT GLIOBLASTOMA**

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**Abstract:** The NoVoTTF-100A device is a portable, home use, medical device which delivers low intensity, intermediate frequency, alternating electric fields (TTFs) to the brain by means of non-invasive, dispos-able scalp electrodes. TTF fields physically interfere with cell division and assembly of organelles (Kirson et al. Carcinogenesis, 2004; Kirson et al. Proc Natl Assoc Sci USA, 2007; Salzberg et al. Onkologie, 2008; Kirson et al. BMC Med. Phys. 2009). METHODS: Adult patients with recurrent GBM were to be randomized (1:1) to either NoVoTTF-100A administered continuously (24–24 hours/day, 7 day/week) or the best local standard of care (BSC) chemotherapy, at the physicians discretion, in each center. Randomization was stratified by prior surgery for recurrence and center. The number of prior treatments was not limited; a Karnofsky performance status of ≥ 70% and an adequate end-organ function were required. The primary endpoint was overall survival; secondary endpoints included 1-y survival, PFS6, TTP, radiological response rate and safety. The study was powered to detect a 60% increase in overall survival (eg, 48 vs 30 weeks) with a two-tailed α of 0.05 and power of 0.80. RESULTS: Between September 2006 and May 2009, 237 patients were included in 28 centers in the United States, Europe, and Israel, 120 patients were treated with NovelTTF-100A alone, and 117 patients received BSC chemotherapies including bevacizumab, nimotuzumab, procarbazine, temozolomide, erlotinib, irinotecan, and imatinib. Meningeal results are to be presented. CONCLUSIONS: This is the first phase III, controlled, clinical trial testing TTF fields, an entirely novel treatment modality in cancer patients. In this trial, it was tested as a single modality in recurrent GBM, and compared with the best available chemotherapy. This treatment holds promise as a single modality in recurrent GBM, and may be well suited for combination with standard chemotherapy.

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

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How the programming and reprogramming of stem/progenitor cells regulate normal brain development and brain cancer is still not well known. One of the tools that we have chosen to investigate stem/progenitor cell regulation is the neuronal transcriptional repressor, RE1-silencing transcription factor (REST). REST is expressed in most neuronal cells, but is absent in most neural cell types. Previously, we found that counteracting REST function by forced activation of REST target genes in NSCs, and even muscle progenitor cells, was sufficient to cause neuronal differentiation, indicating a role for REST in the specification of stem/progenitor cells. Although REST is normally not expressed in most neural cells, we previously found that approximately 50% of human medulloblastomas, a malignant pediatric brain tumor, express REST and that this abnormal expression of REST causes medulloblastoma-like cerebellar tumors by maintaining “stemness” of NSCs. We then found that REST maintains self-renewal and pluripotency in ES cells and this process is regulated by extracellular matrix components. Our recent work indicates that REST regulates self-renewal of normal NSCs and its expression is diminished as NSCs differentiate. Interestingly, a subset of glioblastoma patient sample-derived cancer-initiating cells (glioblastoma stem-like cells or GSCs) expresses abnormal levels of REST. The role of REST in the GSCs is to maintain stemness through a microRNA-mediated mechanism. We are currently working on examining whether REST could function as a therapeutic target in these glioblastoma cell lines. Taken together, the results of our studies indicate that tumor growth is affected by REST expression in neural tumors, that REST regulates self-renewal of normal NSCs and prevents differentiation of glioblastoma stem-like cells.
O.12. EFFICIENT ENGRAFTMENT OF MGMTPT140K GENE-MODIFIED CD34+ CELLS FOLLOWING NONMYELOBLASTIC BCNU CONDITIONING IN PATIENTS WITH GliOBLASTOMA
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BACKGROUND: Glioblastoma, the most common adult primary malignant brain tumor, confers poor prognosis (median survival of 15 months) notwithstanding aggressive treatment. Combination chemotherapy, including carmustine (BCNU) or temozolomide (TMZ) with the MGMT inhibitor O6-benzylguanine (O6BG) has been used, but has associated with dose-limiting hematotoxicity. OBJECTIVE: To assess safety and efficacy of a retroviral vector encoding the O6BG-resistant MGMTPT140K gene for transduction and autologous transplantation of hematopoietic stem cells (HSCs) in MGMT unmethylated, newly diagnosed glioblastoma patients in an attempt to chemoprotect bone marrow during combination O6BG/TMZ therapy. METHODS: Three patients have been enrolled in the first cohort. Patients underwent standard radiation therapy without TMZ followed by G-CSF mobilization, apheresis, and conditioning with 600 mg/m2 BCNU prior to infusion of gene-modified cells. Posttransplant, patients were treated with 28-day cycles of single dose TMZ (472 mg/m2) with 28-day cycles of single dose TMZ (472 mg/m2) bolus, then 30 mg/m2/d. RESULTS: The BCNU dose was nonmyeloablative with ANC < 500/µL for ≤ 5 d and nadir thrombocytopenia of 28,000/µL. Gene marking in pre-infusion colony forming units (CFUs) was 70.6%, 79.0%, and 74.0% in Patients 1, 2, and 3, respectively, by G418/TK-PCR, gene marking in white blood cells and sorted granulocytes ranged between 0.37–0.84 and 0.33–0.83 provirus copies, respectively, by real-time PCR. Posttransplant gene marking in CFUs from CD34-selected cells ranged from 28.5% to 47.4%. Patients have received 4, 3, and 2.2 cycles of O6BG/TMZ, respectively, with evidence for selection of gene-modified cells. One patient has received a single dose-escalated cycle at 590 mg/m2 TMZ. No additional hematotoxicity has been observed thus far and all three patients exhibit stable disease at 7–8 months subsequent follow-up.

CONCLUSIONS: We believe that these data demonstrate the feasibility of achieving significant engraftment of MGMTPT140K-modified cells with a well-tolerated dose of BCNU. Further follow-up will determine whether this approach will allow for further dose escalation of TMZ and improved survival.

MOLECULAR MARKERS I

O.13. MOLECULAR MALIGNANT PROGRESSION IN GLIOMAS: ELUCIDATING THEIR GENETIC “LIFE STORY”
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Up till now, typing and grading of diffuse gliomas is based on histopathological features. However, because of, especially, lack of unequivocal criteria and sampling, the robustness of this classification is suboptimal, and more objective tools are needed for more reliable assessment of their biological behavior (eg, nearly all low-grade diffuse gliomas eventually progress to high-grade malignancy); however, time to progression varies considerably and there is currently no valid parameter that unambiguously predicts how rapidly malignant progression will occur. Over the last decades it has become increasingly clear that molecular genetic markers are helpful in recognizing more uniform subgroups of gliomas (eg, loss of chromosome 1p and 19q is reported to predict longer survival and better response to chemotherapy whereas methylation of the MGMT gene predicts chemosensitivity to alkylating agents). Furthermore, several genes were reported to be involved in malignant progression of gliomas; however, detailed information about their “timing” and cooccurrence in the course of molecular progression is relatively lacking. We therefore evaluated a spectrum of over 300 diffuse gliomas the (co-)occurrence of copy number changes involving chromosomal losses (partial or isolated losses) which warrants an accurate identification, separating them from those indicative of a favorable biological behavior (codeletion of complete 1p and 19q). We are currently evaluating the clinical relevance of identification of molecular malignancy as proposed, and preliminary results indicate that this scheme will be helpful for establishing a risk-profile for individual glioma patients and thereby ultimately aid in therapeutic decision-making.

O.14. COMPARISON OF MS-PCR, METHYLIGHT, PYROSEQUENCING, MGMT IMMUNOHISTOCHEMISTRY FOR MGMT ANALYSIS
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MGMT status is a predictive factor of response to standard treatment of newly diagnosed glioblastomas involving temozolomide (TMZ) and radiotherapy, and is used as a prognostic factor because of its becoming a crucial biological marker in new clinical glioma trials, and is beginning to be used in routine clinical practice, there is a strong need to determine the best technique for MGMT analysis. In a French multicenter study, we compared 5 techniques: classical MS-PCR, Methylight, pyrosequencing (PYR), MS-HRM, and immunohistochemistry (IHC). Each technique was centrally performed at an expert center. To analyze the reproducibility of MGMT methylation assays, 3 primary cell lines (GB2/MB2 and GB3) were tested in 10 separate series. GB2 and GB3 were never methylated (Meth) with either MethyLight or MS-HRM, but were Meth in 7 of 10 and 9 of 10 cases with MS-PCR, respectively, while methyl methylation levels were 5% and 9% for PYR, with reproducibilities of 11% and 6%, respectively. GB2M2 was always Meth with MS-HRM and MS-PCR, methylation levels being 42% and 77% for MethyLight and PYR, with reproducibilities of 72% and 7%, respectively. A good linearity was observed for each technique (after sequential mixing of 100% and 0% methylated samples) with detection of levels as low as 2.5%. For IHC, slides from two selected blocks were immunostained and analyzed in 6 different series. The number of positive cells ranged from 8% to 60% (mean 31%) in 1 case and from 3% to 20% (mean 8%) in the other. Following tests on 99 samples from patients with newly diagnosed GBM treated with standard treatment (radiation and TMZ), the best predictive values for overall survival were obtained by PYR (P < .0001), MS-PCR (P < .00001), and IHC (P < .001). MethyLight (P = .09) and MS-HRM (P = .03) yielded disappointing results in this series of patients. Contrary to recent studies, MGMT expression assessed by IHC was well correlated with overall survival. As observer variability is a reported problem with this technique, which could account for the poor reproducibility observed in this study, stained slides are currently evaluated by 2 other pathologists to validate the result. For MGMT promoter methylation analysis, PYR appears to be a very robust technique and a good alternative to classical MS-PCR, which is not well adapted to clinical practice. The next step of the project aims at implementing these techniques in different laboratories.

O.15. TRANSCRIPTIONAL INACTIVATION AND PROMOTER HYPERMETHYLATION OF THE TUMOR SUPPRESSOR GENE NDRG2 IN HIGH-GRADE OLIGODENDROGLIAL TUMORS
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BACKGROUND: The NDRG2 gene is a member of the N-myc downstream-regulated gene family that is located on chromosome 14q11.2. It has been proposed that the NDRG2 gene is a candidate tumor suppressor gene (TSG), which, when inactivated by hypermethylation, shuts off the autocrine growth-promoting activity and promotes cell differentiation. Consistent with its potential function as a TSG, downregulation...
of NDRG2 expression is found in several human cancer cell lines and tissues, including meningiomas and glioblastomas (GBs). AIM: A gene expression profiling analysis to identify differentially expressed genes between high- and low-grade glioblastomas (OGs). RESULTS: The human gliomaoma samples consisted of 15 GBs (WHO grade IV) and 59 oligodendrogliomas (OTs), including 19 WHO grade II oligodendrogliomas (OGs), 16 WHO grade III OGs, 11 WHO grade II mixed oligoastrocytomas (OAs), and 13 WHO grade III OAs. mRNA expression levels were measured by quantitative real-time reverse transcriptase PCR high-throughput analysis. Promoter hypermethylation was determined by sodium bisulfite-modified treated DNA followed by methylation-specific PCR. RESULTS: Low mRNA expression levels relative to non-tumoral brain tissue were detected in 52% (5 of 10) of high-grade OTs, and 92.3% (12 of 13) of GBs. In contrast, only 7.1% (1 of 14) of low-grade OTs showed NDRG2 reduced mRNA expression levels, Promoter hypermethylation was detected in 38.5% (10 of 26) of high-grade OTs, as well as in 58.8% (10 of 17) of GBs, while none of the low-grade OTs showed NDRG2 promoter hypermethylation. Likewise, there was a significant correlation between the low RNA expression levels and/or the promoter hypermethylation of NDRG2 and high-grade OTs (p = 0.455; P < .01). CONCLUSION: Taken together, our results suggest inactivation of NDRG2 in high-grade OTs through hypermethylation of its promoter region, which points out its role as a TSG. In addition, NDRG2 inactivation may be a useful biomarker to predict a more aggressive behavior in OTs.

O.16. A FOUR-GENE SIGNATURE ASSOCIATED WITH CLINICAL OUTCOME IN HIGH-GRADE GLIOMAS
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Molecular studies of high-grade gliomas (HGGs) have highlighted the heterogeneity of these tumors, and have linked molecular signatures to clinical outcomes. This work aimed to develop a prognostic model to identify such molecular subtypes of tumors is essential for guiding therapeutic advances. We report the development and validation of a robust risk-score model highly associated with the outcome of patients with high-grade gliomas. We performed a meta-analysis of HGGs microarray studies (n = 96) and reported here the development and validation of a robust risk-score model associated with outcome. We performed a meta-analysis of HGGs microarray data sets (267 patients) to identify such biomarkers from a robust signature related to tumor aggressiveness. These biomarkers were used to construct a risk-score model. The model was associated with overall survival (OS) and with good discrimination (C-statistic) was based on the expression of 4 genes. Patients were ranked according to their risk score and stratified into 2 groups. Low-risk score patients had a median OS longer than high-risk score patients (46.6 vs 11.7 months, P < .001). These results were validated on an independent microarray study of 59 patients. We performed RT-qPCR validation on an independent set of HGGs (194 patients) and compared the performances of our risk-score model with the prognostic estimates revealed a borderline significant survival benefit for patients who lacked tHERT expression in a median survival of 20.1 vs 14.7 months for patients with high tHERT expression (P = 0.05). Tumor tissue was associated with longer overall survival in glioma patients, indicating that tHERT might have quality as prognostic biomarker predicting tumor aggressiveness.

O.18. IDH1 MUTATIONS IN GLIOMAS: CORRELATION WITH GENOMIC PROFILE AND PROGNOSIS
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Recently, IDH1 codon 132 mutations (mostly Arg132His) have been found in gliomas, resulting in the loss of normal isocitrate dehydrogenase activity and the acquisition of an alpha-ketoglutarate reductase activity. Rarely, they are found in patients under 50 years of age. The prognosis of patients affected by these tumors is favorable compared with the prognosis of patients with IDH1 wild-type gliomas. The purpose of this study was to evaluate the incidence of IDH1 mutations in gliomas and to evaluate their impact on the genomic profile and outcome of patients. We used direct sequencing and new PCR approaches such as COLD PCR (complimentation at lower denaturation temperature–PCR) combined with high-resolution melting (HRM) to detect IDH1 mutations. We identified a mutation rate of 3% in 2272 glioma tumor samples. Forty-seven (4%) of the mutations were IDH1/2 mutations. In grade II–IV gliomas, IDH1/2 mutations were inversely correlated with grade, affecting 12% (67%) grade II, 33% (17%) grade III, and 36% (13%) grade IV gliomas. The IDH1 mutation was tightly related to the 1p19q codeleted group and MGMT methylation, but mutually exclusive with EGFR amplification (2.5% IDH1 mutated 4 of 177). Strikingly, all the 1p19q codeleted gliomas were mutated on IDH1 (92%) or IDH2 (8%). IDH1 mutation was associated with a better outcome in grade II (14.5 vs 92.0 months, P = 0.002).
ABSTRACTS

O.19. PROSPECTIVE MULTICENTRIC VALIDATION OF A SURVIVAL PROGNOSTIC INDEX IN LEPTOMENINGEAL CARCINOMATOSIS: ANALYSIS INTERIM OF THE ACME STUDY
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INTRODUCTION: Leptomeningeal carcinomatosis (LC) represents a devastating complication of systemic cancer. Although median survival is short despite therapy, up to 10–20% of patients can achieve 1-year survival with treatment. To decide which patients should be treated is difficult. To help in the decision of which patients are best candidates to be treated, a survival prognostic index (PI) was developed. The ACME study is conducted to validate this PI. The aim of this report was to present the preliminary results. PATIENTS AND METHODS: The enrolment was initiated on June 2008 and recruitment period will finish on June 2010, participating 29 Spanish centers. LC diagnosis is based on the presence of positive cytology on cerebrospinal fluid (CSF) or CSF biochemical abnormalities associated with suggestive clinical and magnetic resonance. Clinical data, CSF parameters, tumor-related characteristics, and treatment information are recorded. PI is composed by 3 prognostic variables: Radiation Therapy Oncology Group (RTOG) neurological scale ≤2, glucose level in CSF ≥2.7 mmol/L, and presence of intraterrororal syndromes. Each variable is scored as 0 or 1, according to the absence or presence. Group of unfavorable PI includes patients who score ≤2 points. The impact of single parameters on overall survival is determined by both univariate and multivariate analysis. RESULTS: Up to now, 73 patients are enrolled. Data from the first 46 patients included with complete follow-up was analyzed. Thirty-four patients received intrathecal with or without systemic chemotherapy. Univariate analysis identified female sex, breast cancer, Karnofsky Performance Status, negative CSF cytology, PI, and treatment (intrathecal with or without systemic chemotherapy) as parameters that influenced prognosis. Median survival was 7.0 months (interquartile range 5.1–10.5 months) and 1-year survival was 20.6% (95% CI 13.7–27.6). The explantation of this preliminary analysis confirm PI as useful prognostic score in LC patients. PI includes patients who score 1.33–11.11, P ≤ 0.012, treatment (HR: 7.14; 95% CI: 2.5–20, P ≤ 0.001), and PI (HR: 2.77; 95% CI: 1.1–7.14, P = .031) were associated independently with longer overall survival in LC patients. CONCLUSION: Preliminary results confirm PI as useful prognostic score in LC patients. Moreover, breast cancer and a negative cytology on CSF also emerge as good independent prognostic factors.

O.20. NEOPLASTIC MENGITIS: VALUE OF MRI AND PROTEIN ANALYSIS AND PATTERNS OF LYMPHOMATOUS CYTOMORPHOLOGY
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INTRODUCTION: Neoplastic meningitis (NM) from lymphoma or leukemia, is still difficult to detect. With cytology, one key diagnostic procedure, neoplastic lymphocytes are difficult to distinguish from inflammatory lymphocytes. We evaluated here whether specific morphological criteria can improve this differentiation. Moreover, we assessed the sensitivity of MRI and protein analysis for the detection of all kinds of NM in comparison with CSF cytology.

O.21. CASE SERIES OF FRAMELESS LINEAR ACCELERATOR-BASED STEREOTACTIC RADIOSURGERY TO THE POSTOPERATIVE RESECTION CAVITY FOR BRAIN METASTASIS: AN INITIAL REPORT OF OUTCOMES AND PATTERNS OF FAILURE
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BACKGROUND: Whole-brain radiotherapy (WBRT) is the standard of care following resection of a brain metastasis. Lack of a survival benefit and concern regarding possible neurocognitive effects with this approach has led to stereotactic radiosurgery being investigated as an alternative treatment strategy. Radiosurgery is likely to offer effective local control while preserving WBRT for use as a salvage therapy for distant brain failures. We report our initial experience using a linac-based radiosurgery system. We report our single institution outcomes, patterns of failure and the image-guided setup accuracy of the first 15 consecutive cases treated at Brigham and Women’s Hospital using image-guided (Excactrac by Brainlab) linear accelerator-based radiosurgery with a relocatable stereotactic frame and aquaplast mask (BrainLAB Mask System). The target volume was the resection cavity without a margin, excluding the surgical track. Median number of brain metastasis per patient was 1 (range 1–3). Median planning target volume was 3.3 cm² (range 0.35–10.8 cm²). Median prescribed dose was 18 Gy with normalization ranging from 69 to 81%. Ninety-nine percent of the PTV was covered by the prescribed dose in all cases. Mean conformity index was 1.62 (range 1.41–1.92). RESULTS: At a median follow-up of 8.2 months (interquartile range 3.7–12.1 months) local control was achieved in 13 of 14 cases. True local recurrence occurred in 1 case. No marginal failures occurred. Distant brain failure occurred in 5 of 14 cases. Median time to any failure was 7.5 months. Salvage therapy was administered to patients (3 received WBRT, 1 received further radiosurgery, and 1 received systemic therapy only). No grade 3 or higher toxicity was recorded. Factors associated with lack of CNS failure (local or distant) included a single brain metastasis and long interval between initial cancer diagnosis and the development of brain metastasis. The frameless image-guided radiosurgery was delivered with submillimeter accuracy. The mean residual setup error was 0.45 mm (SD = 0.19 mm) and the mean intrafraction motion was 0.37 mm (SD = 0.31 mm). CONCLUSIONS: Image-guided frameless stereotactic radiosurgery to the resection cavity following surgery for a brain metastasis is a safe and accurate technique that offers durable local control and postpones the use of WBRT in selected patients. This technique should be tested in larger prospective studies.
O.22. TREATMENT OF BRAIN METASTASES FROM NON–SMALL CELL LUNG CANCER WITH WHOLE-BRAIN RADIOTHERAPY (WBRT) IN COMBINATION WITH Gefitinib (GFT) OR TEMOZOLOMIDE (TMZ): A RANDOMIZED Multi-Centre Phase II Trial of the Swiss Group of Clinical Cancer Research (SAKK #70/03)

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BACKGROUND: Patients with BM rarely survive >6 months and are commonly excluded from clinical trials. We aimed at improving outcome by exploring 2 combined modality regimens with at the time novel agents for which single-agent activity had been shown. METHODS: NSCLC patients with multiple BM were randomized to WBRT (10 x 3 Gy) and either GFT 250 mg p.o. daily or TMZ 75 mg/m^2 p.o. daily x21/28 days, starting on Day 1 of RT and to be continued until PD. Primary endpoint was overall survival, a Simon’s optimal 2-stage design was based on assumptions for the 3-month survival rate. Cognitive functioning and quality of life were also evaluated. RESULTS: Fifty-nine patients (36 M, 23 F; 9 post-prostate chemo) were included. Median age was 61 years (range 46–82), WHO PS 0 was in 18 patients, 1 in 31 patients, and 2 in 10 patients. All but 1 patients had extracranial disease; 33 of 43 (TMZ) and 15 of 16 (GFT) had adenocarcinoma histology. The trial was closed early after stage 1 analysis when the prespecified 3-mo survival rate threshold (66%) was not reached, causes of death were not GFT related. Main causes of death were PD in the CNS (28%), systemic 41%, both 8%, and toxicity 10% (intestinal perforation 2 patients, pneumonia 2, pulmonary emboli 1, pneumonitis NOS 1, seizure 1). We summarize here other patients’ characteristics for the 2 trial arms: TMZ (n = 43)/GFT (n = 16); median treatment duration: 1.6/1.8 mo; Grade 3–4 toxicity: lymphopenia 5 patients (12%)/0; fatigue 8 patients (15%)/2 patients (13%); Survival data for TMZ/GFT arms, 3-month survival rate: 58.1% (95% CI 42.1–73.6)/62.5% (95% CI 35–85); median OS: 4.9 months (95% CI 2.5–5.6)/6.3 months (95% CI 2.2–14.6); median PFS: 1.8 months (95% CI 1.3–1.8)/1.8 months (95% CI 1.1–3.9); median time to neuro. progr.: 8.0 months (95% CI 2.2–X)/4.8 months (95% CI 3.9–10.5). In a model to predict survival time including the variables’ age, PS, number of BM, global QL, total MMS score, and subjective cognitive function, none of the variables accounted for a significant improvement in survival time. CONCLUSIONS: The combination of WBRT with GFT or TMZ were feasible. However, in this unselected patient population, survival remains poor and a high rate of complication was observed. Four patients died as a result of high-dose corticosteroids. Preliminary evaluation of cognitive functioning failed to show significant improvement. Indications and patient selection for palliative treatment should be revisited and careful monitoring and supportive care is required. Research and progress for this frequent clinical situation is urgently needed. Trial partially supported by AstraZeneca (Switzerland), Essex Chemie (Switzerland) and Swiss Federal Government.

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

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BACKGROUND: Neoplastic meningitis (NM) is a devastating neurologic complication of cancer whose frequency and patterns of care are not well known. We investigated in a prospective survey, the frequency, patterns of care, and outcome of NM from solid tumors in a Community Hospital-based regional cancer network. METHODS: Clinical forms to collect tumor and QL signs, neurologic symptoms/signal, radiologic changes, CSF cytology, treatment options, and outcome were sent to 29 neurologic and 42 medical oncology Services of the Regione Piemonte (Italy). Data were centrally reviewed in a University Hospital to confirm the diagnosis and to perform the final analysis. RESULTS: From December 2007 to December 2008, we enrolled 68 patients with suspected NM. Diagnosis was confirmed in 59 patients (87%). Diagnosis was pathologically confirmed in 27 of 59 (46%) patients while was clinico-radiologic in 32 of 59 (54%). There were 39 females and 20 males with a median age of 59 years (range 38–80). The site of primary tumor was breast in 25 of 59 (42%), lung in 18 of 59 (31%), unknown in 5 of 59 (8%), gastrointestinal tract in 4 of 59 (7%), skin (melanoma) in 3 of 59 (5%), miscellaneous in 4 of 59 (7%) patients. The systemic disease at the time of diagnosis of NM was progressive in 59 of 59 (99%) and absent/under control in 4 of 59 (7%) patients. Brain metastases were concomitant in 26 of 54 (47%) patients. The median latency between first symptom and NM diagnosis was 4 weeks (range: 0–26 weeks). Treatment for NM consisted in intrathecal chemotherapy with liposomal doxorubicin (9 of 59 patients), WBRT and local RT (5 patients), TMZ (8 patients), CRT (2 patients), RT + intrathecal chemotherapy (2 of 59), surgical removal of spinal bulky disease (1 in 39), whereas 30 in 59 patients (51%) underwent supportive care only. Median survival was 6.8 weeks. In a multivariate analysis, the only parameter that influenced the prognosis was Karnofsky >60 (P < .0042).

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

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BACKGROUND: Prognosis is poor in patients with relapsed lymphoma with central nervous system (CNS) localization. In chemosensitive-relapsed systemic lymphoma without CNS localization, autologous stem cell transplantation (ASCT) is the treatment of choice and is able to increase the long-term survival rate, especially when combined with rituximab. Small retrospective series on transplanted patients have shown that this treatment is feasible in selected cases with CNS recurrence, but no prospective data are available. Given the rarity of the disease, an international collaboration within the IPCG was formed to obtain data on patients from a variety of countries. METHODS: From affiliated and interested centers performing ASCT, all patients with a CNS localization of systemic lymphoma at first recurrence or progression potentially eligible for ASCT were selected from local databases. Anonymized data were collected on primary disease, recurrence or progression, treatment of recurrence or progression, result and toxicity of this treatment, and survival. RESULTS: From 6 centers in 5 countries, 72 patients were identified. Initial treatment varied but contained intrathecal treatment or prophylaxis in 13 patients, and systemic rituximab in 32. Initial symptoms of the recurrence were of CNS disease in 50 patients, of systemic disease in 7, and of both in 14. In 18 of 59 patients, RT was performed. Overall survival in 36 patients (83%) of patients treated for CNS recurrence only, 36% had a leptomeningeal localization with or without a parenchymal lesion. Patients initially treated with rituximab had an increased risk of CNS parenchymal relapse: 74% compared with 44% in patients who were rituximab naive (P = .014, x^2 test). The site of recurrence was not unique, but 93% of patients was treated with HD-MTX or HD-cytarabine containing regimens. Twenty-four patients were not eligible for transplantation because of age, prior transplantation, or unknown reasons. Of the remaining 48 patients, 17 (35%) received ASCT. Median survival from the time of CNS relapse in all patients was 8 months, and that in transplanted patients >49 months. Survival at 1 year after transplantation was 81%. CONCLUSIONS: Significantly more patients initially treated with rituximab had a CNS parenchymal lesion rather than leptomeningeal localization only. Only 35% of patients potentially eligible for transplantation was transplanted; those reaching transplantation had favorable survival following transplantation.

CELL BIOLOGY/IMMUNOTHERAPY

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

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Hematopoietic progenitor cells (HPCs), but also mature blood cells, are increasingly investigated regarding their role for tumor angiogenesis, with
O.26. NOTCH PATHWAY BLOCKADE AFFECTS THE MIGRATORY AND DIFFERENTIATING CAPACITY OF BRAIN TUMOR INITIATING CELLS
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BACKGROUND: The high-grade glioma, glioblastoma multiforme (GBM) is the most common and aggressive primary brain tumor in adults, and aggressive GBM is associated with a poor prognosis. Effective treatment remains an unmet clinical challenge. The majority of GBM’s is often difficult to operate, because of their location and infiltrative growth pattern, and nonsurgical treatments (chemo- and radiation therapy) are often ineffective. As such, relapse is almost certain and new treatment modalities are urgently needed. Brain tumor initiating cells (TICs) are a population of neural stem cell (NSC)-like cancer cells reported in GBM. TICs are increasingly being assigned a central role in brain tumor initiation, progression, treatment resistance, and relapse and are suggested as a novel target in glioma therapy. The Notch signaling pathway is important in maintaining an undifferentiated state of normal NSC and in determination of cell fate. Components of the Notch pathway are often found aberrantly expressed in GBM. Recent results demonstrate that active Notch signaling is important for the maintenance and growth of GBM-derived TICs. Thus, the Notch signaling pathway might be an appropriate target for GBM therapy targeting TICs. AIM: We investigated the functional role of Notch signaling in TICs by examining the effect of Notch inhibition on tumorigenicity and stem cell-like properties. RESULTS: Primary neurosphere cultures were established from xenografts originally derived from human primary GBM. All cultures were maintained and grown in vitro. These data demonstrate a novel role for Notch signaling in glioma progression.

O.27. NG2 PROMOTES RESISTANCE TO IONIZING RADIATION BY ELEVATED PEROXIREDOXIN-1 AND DNA DAMAGE RESPONSE IN Glioblastoma Multiforme
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Glioblastoma multiforme (GBMs) are lethal cancers that respond poorly to radiotherapy and the mechanisms may involve stem/progenitor cells. Several studies proclaimed that brain tumors enriched in CSCs were preferentially resistant to ionizing radiation and chemotherapy as a result of altered checkpoint and DNA repair pathways compared with conventional tumor cells. Others have claimed that these cells are associated with increased reactive oxygen species and that this is an additional mechanism for radiation resistance. Since the glioblastoma progenitor marker NG2 has been shown to regulate tumor response to chemotherapy, we examined whether it also affected response to radiotherapy. Quantification of NG2 expression in 96 patient GBM biopsies revealed that high expressers had shorter survival outcomes than lower expressors, P = .02. Two-dimensional (2D) proteomics of 11 of these biopsies showed that peroxiredoxin-1 (PRDX-1) was upregulated in the shortest surviving patients, and was associated with reduced oxidative damage. Furthermore, NG2 expressing GBMs were highly resistant to ionizing radiation (IR) in vitro and in vivo and increased PRDX-1 levels in a dose-dependent manner. shRNA-mediated NG2 knockdown in the GBM tumor cells to IR and attenuated dose-dependent induction of PRDX-1. Moreover, NG2 expressing cells rapidly induced DNA damage response signaling as indicated by phosphorylation of H2AX, ATM, and Chk2 proteins compared with NG2 negative cells. PRDX-1 expression was increased in the NG2 knockdown transiently slowed tumor growth rates in vivo and partially sensitized the tumors to ionizing radiation in vitro. These data demonstrate a novel role for NG2 in mediating radiosistance in human GBMs by interaction with PRDX-1 and DNA damage response machinery.

CD44 is a transmembrane receptor for hyaluronan that coordinates intracellular signaling and cytoskeleton rearrangements in response to cues from the extracellular matrix. As brain tumors develop in a hyaluronan-rich environment, overexpression of CD44 can lead to the enhancement of proliferation, migration, and survival facilitated by the Notch signaling pathway. We have developed a murine model of gliomas that is uniquely suited for CD44 loss of function studies. Malignant gliomas were induced in mice by transfecting plasmids encoding SV40LgT and NrasG12V into the lateral ventricle of wild-type (CD44+/+) and knockout (CD44−/−) mice. Tumor progression was monitored weekly using bioluminescent imaging and directly correlated with tumor burden. Grade 3–4 gliomas developed in CD44+/+ mice within 1 month of oncogene delivery. These tumors advanced rapidly as assessed by steadily increasing bioluminescent imaging and a median survival of 39 days. Two-color immunohistochemistry (IHC) was used to detect CD44 expression within the bulk tumor and the infiltrative glioma cells. IHC studies have shown remarkably similar phenotypes of CD44 overexpression in both mouse and human tumor specimens. In addition, CD44 positive tumor cells can be found infiltrating into the plexus of the normal human brain of tumor bearing mice. In contrast to CD44+/+ rapid tumor growth, CD44−/− tumors have a significant delay in progression (median survival = 50 days). Importantly, a subset of tumors in CD44+/+ mice spontaneously regressed measured by bioluminescence. CD44 loss of function was rescued by expressing murine CD44 cDNA in cis to NrasG12V. The significant extension of survival in CD44−/− mice is abolished when CD44 expression is rescued exclusively in the tumor cells. These glioma cells require CD44, rather than CD44 expression, for a microenvironment to facilitate tumor initiation and progression. Our results demonstrate that loss of CD44 impedes the development of malignant gliomas. Furthermore, the spontaneous regression of CD44−/− mice suggests that CD44 may be crucial for maintaining a niche supportive of tumor cell self-renewal and survival. Ongoing studies will look at CD44 modula- tion of multidrug transporter activity and sensitivity to chemotherapeutic agents because of loss of function of CD44.
Glioblastoma multiforme (GBM) is a lethal subgroup of intracranial tumors with a median survival of 14.6 months, despite multimodal treatment. We have previously shown that several treatment resistant tumors aberrantly express the neural progenitor marker NG2. We therefore aimed to target NG2 in GBMs using the 9.2.27 mAb and adoptively transferred autologous natural killer (NK) cells and to determine the immunogenicity of anti-tumor the effect. The NK cells and mAb were infused intratremously by convection-enhanced delivery (CED) in rat brains transplanted with human GBM xenografts, as well as syngeneic rat gliosarcoma. Magnetic resonance imaging was used to longitudinally monitor the tumor growth characteristics. Combined NK + mAb targeting resulted in significantly longer survival times compared with the vehicle, and monotherapy controls (log-rank test, \( P < 0.0001\); \( P = 0.0003\), Histological analyses revealed strong presence of MPO, granzyme, and IFN\(\gamma\)-expressing granulocytic cells in focal areas of strong necrosis/apoptosis in the NK + mAb- and mAb-treated groups. Moreover, double-labeling revealed the greatest numbers of MI-type macrophages that were ED1\(+\), positive that penetrated deep into the tumor of the NK + mAb-treated animals. Flow cytometric analysis revealed less M2 phenotype macrophages in this group compared with the monotherapy controls. Animals treated with NK cells recruited only uniformly double ED1\(+\), CD8\(+\) positive cells that were less abundant and remained in the tumor brain boundary. MRI revealed tumor growth arrest in many NK + mAb-treated animals, whereas mAb-treated tumors displayed reduced contrast enhancement and necrosis. In conclusion, combined 9.2.27 mAb and NK cell therapy strongly affected tumor growth and vascular parameters and prolonged survival. Thus, adoptive cell therapy with NK cells may be an amenable therapy for treatment-resistant GBMs.
controls. Two patients (9%) had a partial response. No patients had a worsening of the visual function. If we considered only the patients with a partial deficit of the sight or visual field, 60% showed an improvement. CONCLUSIONS: OnSMM frameless stereotactic radiotherapy is found to be safe and effective. Tumor growth control was complete and visual function was maintained or improved. If the long-term follow-up will sustain the preliminary results, stereotactic radiotherapy could become the new first-choice treatment.

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

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

O.34. SECOND-LOOK SURGERY (SLS) FOR EPENDYMOMA: THE ITALIAN EXPERIENCE

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

O.35. THIRTY-FIVE YEARS OF SURGICALLY TREATED PEDIATRIC MENINGIOMAS IN THE NETHERLANDS: A DESCRIPTIVE EPIDEMIOLOGICAL CASE STUDY

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OBJECTIVE: To review and describe the epidemiology and the clinical, radiological, pathological, and management profile of all pediatric meningiomas surgically treated during the last 35 years in the Netherlands. MATERIAL AND METHODS: All pediatric patients (~18 yr of age) with the diagnosis meningioma, treated at one of the neurosurgical centers in the Netherlands during the last 35 years, were identified in the PALGA database, the nationwide network, and registry of histo- and cytopathology. Data were retrieved from clinical records, radiological findings, operative reports, and pathological examinations. RESULTS: In total, 115 registries of meningioma histology in pediatric patients were identified in the PALGA database. Forty-six cases were excluded because either the histological diagnosis was a revision and confirmation of the original histology, or the original histological diagnosis was changed after revision. Thus, 69 patients (37 males) were included, making this the largest study of its kind. Clinical presentation: the most common symptom was raised intracranial pressure (30%). Mean age at diagnosis was 11.7 yr (0.3–18.8). Location; most frequently on the convexity (22%). Etiology: 11 patients (16%) had neurofibromatosis type 2 and 4 patients received prior radiotherapy. Histology: 42 patients (61%) had a WHO grade I, with meningotheliomatous meningioma as most common histological subtype. Five patients (7%) had a WHO grade III tumor. Surgery: macroscopic total resection was accomplished in 31 patients (42%) and sub-total in 10 patients (30%). Simple decompression was used in 5 patients (7%). Resection grade was missing in 14 patients (21%). Additional treatment: 15 patients (22%) received radiotherapy postoperatively. Follow-up: mean follow-up was 4.9 yr (~0–27.8). A total of 22 radiological confirmed recurrences were diagnosed in 13 patients (19%) in an interval period of 3.9 yr (0.1–26.3). Eleven tumors recurred after macroscopic total resection. Nine patients with a recurrent tumor were first diagnosed with a WHO I (69%), none with a WHO III tumor. Six patients (9%) died as a result of their meningioma. CONCLUSION: Pediatric meningiomas are extremely rare. This is the first single-country study and one of the largest childhood series on this tumor. The presentation and biological behavior is different compared with meningiomas in adults. A high recurrence rate is observed and outcome tends to be worse.

O.36. DOSE CONSTRAINT MODEL TO PREDICT NEUROCOGNITIVE OUTCOMES IN YOUNG PATIENTS WITH LOW-GRADE BRAIN TUMORS TREATED WITH STEREOTACTIC CONFORMAL RADIOTHERAPY

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BACKGROUND: To analyze the effect of radiotherapy (RT) dose levels on various brain structures as a model to preserve neurocognition in young patients with low-grade brain tumors treated prospectively with stereotactic conformal radiation therapy (SRT). MATERIALS AND METHODS: Thirty-five patients (median age 13 yr) with low-grade and benign residual/progressive brain tumors (craniopharyngioma, cerebellar astrocytoma, choroidal hypotalamic glioma, other low-grade glioma) were
BBB breakdown has taken place, we hypothesized that this molecule may play a significant role in the development of cerebral capillaries with BBB properties. The homologue Glut1 amino sequence in zebrafish is highly similar to that of humans, therefore the zebrafish is eligible as a model organism for the investigation of the human Glut1 gene. In our zebrafish model of Glut1 knockdown, the development of the cerebral microvasculature appeared to be interrupted with reduced expression of the Tj/Aj proteins and induction of transient brain edema. The data provide the first functional assessment of the role of Glut1 in the development of the cerebral capillary endothelium in vivo and suggest a crucial role of this molecule in the development of the cerebral microvasculature and formation of the BBB. Therefore, modulation of Glut1 expression and function may well be important clinical implications for the development of novel therapeutic avenues toward recovering BBB disruption in devastating brain disorders.

O.39. TIMP-1 AND THE TIMP-1 INTERACTING CELL SURFACE PROTEIN CD63 IN CULTURED ASTROCYTOMA DERIVED SPHEROIDS: EXPRESSION AND CO-EXPRESSION WITH STEM CELL MARKERS
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In previous studies, we have shown that the immunohistochemical expression of TIMP-1 (tissue inhibitor of metalloproteinases-1) and CD63 increases with tumor grade in astrocytomas grade II–IV. Moreover, we demonstrated that a high TIMP-1 protein expression in glioblastoma was associated with a shorter overall patient survival. Recent studies have suggested that TIMP-1 can prevent chemo-induced apoptosis and in a study, using human breast epithelial cells (MCF10A), it was demonstrated that the interaction of TIMP-1 and CD63 is necessary for the TIMP-1 anti-apoptotic pathway. The aim of the present study was to investigate the expression of TIMP-1 and CD63 in cultured organotypic multicellular spheroids (OMS) and cell line spheroids (CLS) derived from astrocytomas in order to assess spheroid models for future studies involving TIMP-1, CD63, and chemo-resistance. By investigating the spheroids immunohistochemically, we wanted to elucidate whether TIMP-1 and CD63 are co-expressed within the spheroids and whether they are expressed by tumor stem-like cells, since these cells are known to be more resistant to chemotherapeutic treatment. In the present study, OMS from 9 astrocytomas and CLS from 3 commercial astrocytoma cell lines were included as well as the glioblastoma tumor stem cell line SJ-1 made in our laboratory. In general, high levels of CD63 protein were detected in all the original tumors, whereas TIMP-1 was more weakly expressed. TIMP-1 and CD63 expression was performed on selected OMS and CLS showing tumor cells expressing both proteins. Furthermore, double staining was performed with TIMP-1 and the stem cell markers CD133, nestin, and Sox2, demonstrating that a population of the tumor stem-like cells expressed TIMP-1. In conclusion, this study shows that spheroid models can be used in future studies investigating the role of TIMP-1 and CD63 in chemo-induced apoptosis. Furthermore, these results indicate that a fraction of the tumor stem-like cells could be protected by TIMP-1–CD63 interaction.

O.40. MYELODYSPLASIA IN PRIMARY BRAIN TUMOR PATIENTS TREATED WITH ALKYLATING AGENTS
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BACKGROUND: Treatment–related myelodysplastic syndrome (t-MDS) and acute myelogenous leukemia (t-AML) represent rare secondary events in patients with primary tumors of the nervous system. The emergence of temozolomide as an effective alkylating agent with little acute toxicity or significant myelosuppression as a long-term treatment strategy led to increased use of chemotherapy for many patients with malignant and even low-grade infiltrative gliomas. In the absence of solid incidence data, we were interested in reviewing the published experience of t-MDS/t-AML in this patient population. METHODS: Case reports and small case series of patients with t-MDS and t-AML during or after treatment with alkylating chemotherapy for a primary brain neoplasm were identified through a comprehensive search of the PubMed
database of the US National Library of Medicine. We recorded type of alkylating and other chemotherapy agents used, dose, concomitant or sequential irradiation, genetic predisposition, type of myelogenous tumor, cytogenetic findings, latency between completion of chemotherapy and diagnosis of t-MDS/t-AML, treatment, and outcome. RESULTS: We identified 39 cases fulfilling eligibility criteria. There were 17 male and 16 female patients (gender not listed in 6) with a median age of 20 years [range 0.25–69 yr]. The most common primary tumor was anaplastic astrocytoma (9) followed by medulloblastoma, low-grade astrocytoma (6 each), glioblastoma (5), and choroid plexus papilloma (3). Twenty-eight patients developed t-MDS. Of those, 12 progressed to t-AML. In 11 patients, t-AML was the first hematologic diagnosis. Median interval between completion of chemotherapy and diagnosis of t-MDS/t-AML was 17 months [range 0–29 months]. Patients received lomustine, carmustine, nimustine, procarbazine, temozolomide, (VEGF) in radiation necrosis (RN) of the brain from a pathological and clinical and molecular genetic evaluation. Histopathology was confirmed. FET-PET analysis reached a sensitivity of 92% and a specific heterogeneity FET uptake kinetic was found throughout tumor volumes and a plastic focus. CONCLUSION: Homogeneous or heterogeneous glioma histology was confirmed. FET-PET analysis reached a sensitivity of 92% and a specificity of 82% in determination of an anaplastic focus. Eleven out of 14 tumors with heterogeneous histopathology were MGMT methylated specificitiy of 82% in determination of an anaplastic focus. Eleven out of 14 tumors with heterogeneous histopathology were MGMT methylated.

O.4.4. HOT SPOTS IN 18FET-PET DELINATE MALIGNANT TUMOR PARTS WITHIN SUSPECTED WHO GRADE II GLIOMA
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OBJECTIVE: This prospective study correlates metabolic maps of intratumoral [F-18]fluoroethyltyrosine (FET) uptake kinetic with detailed histopathology and molecular genetic profiling in untreated adults with magnetic resonance imaging (MRI)-based suspicion of a WHO grade II glioma. Special attention was set on diagnostic accuracy of FET-PET in noninvasive delineation of an anaplastic focus. METHODS: Individual maps of FET uptake kinetics were generated and metabolic hot spots were outlined three dimensionally. Novel 18FET-PET-guided serial stereotactic biopsy procedures were found suitable for stepwise histopathological and molecular genetic evaluation. Histopathology was done according WHO criteria by independent observers. O-Methylguanine-DNA methyltransferase (MGMT) promoter methylation was determined by methylation-specific polymerase chain reaction/sequencing and isocetate dehydrogenase (IDH1/2) mutations by immunohistochemistry analysis, respectively. RESULTS: A total of 373 biopsy samples from 55 consecutive patients were analyzed. In 24 patients, 14 patients with IDH1/2 mutated glioma, four cases were homogeneous for anaplastic focus. CONCLUSION: FET-PET analysis reached a sensitivity of 92% and specificity of 82% in determination of an anaplastic focus. Eleven out of 14 patients with heterogeneous histopathology were MGMT methylated and 9 patients showed IDH1/2 mutations. Both mutations were homogeneously distributed throughout each tumor irrespective of an anaplastic focus. CONCLUSION: Homogeneous or heterogeneous glioma histology can be precisely delineated by dynamic FET-PET evaluation; an anaplastic focus can be reliably identified. Our finding has implications for prognostic evaluation, biopsy planning, and individualized treatment strategies.
O.44. LANGUAGE MAPPING FINDINGS AND CORRELATION WITH DTI–FT DATA DURING SURGICAL REMOVAL OF LESIONS INVOLVING LANGUAGE AREAS OR PATHWAYS

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Surgical resection of lesions involving language areas or pathways requires intraoperative identification of functional cortical and subcortical sites to effectively and safely guide resection. Diffusion tensor imaging (DTI) and fiber tractography (FT) are magnetic resonance (MR) techniques based on the concept of anisotropic water diffusion in myelinated fibers, which allow three-dimensional reconstruction and visualization of white matter tracts, and provide information about the relationship of these tracts with the tumor mass. We have routinely used DTI–FT to reconstuct various tracts involved in the language system [superior longitudinalis (SLF), inferior fronto occipitalis (IFO), inferior longitudinalis (IFL), uncinatus (UNC), premotor fibers] in a series of 305 patients with gliomas (mostly low grade) involving the language areas or pathways. DTI–FT information were loaded into the neuronavigational system and combined intraoperatively with those obtained with direct electrical stimulation applied at subcortical level, with bipolar electrical stimulation (DES). In this work, we report the results of such experience, describing the findings for each tract and discussing technical aspects of the combined use. Large part of SLF was located inside the tumor mass and highly infiltrated by it, and can be safely resected because not functional. IFO was a discrete fasciculus and, when identified intraoperatively, was functional in most of the cases. IFL was located at the lateral portion of temporal tumors and identified as a separate tract in functional in small tumors. The temporal portion on UNC could be removed, whereas the frontal portion had to be preserved to keep language functional integrity. Premotor face fibers must be reconstructed, identified, and preserved intrasupratentorially to avoid anarthry. Tract identification was associated with a 79% chance to develop early postoperative deficits. The rate of definite deficits (at 1 mo) was <2%. The rate and speed of recovery in the postoperative period correlated with the subcortical organization of some of the tracts, such as the SLF, and could be predict preoperatively. The combined used of DES and DTI–FT allowed to effectively and safely trace language tracts, reduced duration of surgery, patient fatigue, and kept a high rate of patient functional integrity.

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

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PURPOSE: In meningiomas which are considered to be benign brain tumors, there are malignant-type tumors. Most of these malignant-type meningiomas are histologically diagnosed anaplastic or atypical ones. However, some of malignant-type meningiomas show poor clinical courses, although histological diagnoses are benign. It is difficult to distinguish this specific group from usual benign-type meningioma. Therefore, we tried to gain characteristic extraction by the metabolite expression profiling using nuclear magnetic resonance (NMR)-based metabolomics (comprehensive metabolite analysis). METHODS: We extracted water and lipid soluble metabolites from recent frozen surgical specimens which are 31 meningiomas, including 2 anaplastic-, 1 atypical-, and 2 malignant-type cases, and measured1H-NMR spectra. Then, we did analysis by data-processing software Alice2 for metabolomeTM ver1.0 (JEOL DATUM) and ADOMWORKS/ModellBuilder ver.3.1 (Eurisearch). For the parameters which characterized malignancy in loading plot. RESULTS: Water soluble metabolites: Surgical specimens were distributed to almost 2 domains (grade 1 and grade 2/3/5 domains). Two anaplastic and 1 atypical meningiomas were distributed the same domain, and malignant-type and anaplastic-type were distributed over extremely near location in the grade II/III domain. Lipid soluble metabolites: Malignant-type meningiomas were distributed near location in the grade III domain. However, grade II domain was isolated. CONCLUSION: This study suggests that NMR-based metabolomics are very useful for prediction of malignant-type meningiomas that were histologically benign.

O.46. INTRAOPERATIVE AND INTEROBESERVER AGREEMENT IN VOLUMETRIC ASSESSMENT OF GLOBLASTOMA MULTIFORME RESECTION

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OBJECTIVE: The aim of this study was to analyze intraoperative and interobserver agreement of manual segmentation as a method for volumetric assessment of glioblastoma multiforme (GBM) resection. METHODS: Three observers performed volumetric assessment of preoperative tumor volume (PreTV) and postoperative tumor volume (PostTV) by manual segmentation on contrast-enhanced T1-weighted magnetic resonance imaging (MRI). Data sets of patients. Measurements were repeated after an interval of minimum 2 weeks. Intraobserver and interobserver agreement were assessed using PreTV, PostTV, and residual tumor volume percentage (RTV) were expressed in intraclass correlation coefficients (ICC). RESULTS: Intraobserver agreement is high for PreTV (ICC = 0.99), PostTV (ICC = 0.73–0.94) and RTV (ICC = 0.54) and low for PostTV (ICC = 0.54) and RTV (ICC = 0.52). CONCLUSION: Volumetric assessment of GBM resection seems to offer high intraobserver agreement, but low interobserver agreement. The results suggest that intraobserver agreement is good, but interobserver agreement is low. Further research is needed before this method can be used as a valid endpoint for clinical studies.

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

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INTRODUCTION: 18F-fluorothymidine (FLT) is a tracer for positron emission tomography (PET) depicting tumor cell proliferation. Quantitative analysis by calculating maximum standardized uptake value (SUVmax) has been shown to correlate with the Ki-67 index, time to progression, and overall survival. For estimating the proliferative tumor volume (PTV), different PET segmentation methods can be used. The aim of this study was to identify the method that best predicts overall survival. MATERIALS AND METHODS: Three different segmentation methods for estimating the PTV were used. The 50% isocount of the SUVmax signal was used to estimate PTV50%. The signal-to-background (SBR) ratio was used as an adaptive threshold delineation (PTVadap) method. The iterative background-subtracted relative threshold level method was used to estimate PTVrel. The Cox proportional hazard regression model was used to assess the significance of the SUVmax and the different PTVs on survival. Receiver-operating-characteristic (ROC) curve analysis was used to identify the threshold for patients with longer survival. Kaplan–Meier analysis and log-rank statistical test were used to test the power of FLT–PET for predicting survival. RESULTS: Twenty-two patients had a diagnosis of glioblastoma multiforme, 2 of anaplastic oligodendrogloma, 1 of anaplastic ependymoma, and 1 of anaplastic astrocytoma. The tumor was resected in 17 patients and 9 patients received a biopsy. The mean age was 52 years (range 35–67 years), and 20 patients were male. The mean overall survival was 411 days (min. 51 days, max. 881 days, SD 262) and 19 patients died during the follow-up period. The PTV50% was associated with a significant better survival (P = 0.03) compared with the PTV50% and SUVmax. ROC analysis found a threshold volume for the PTV50% of 11.4 cc (sensitivity 68%, specificity 71%). Kaplan–Meier analyses showed a significant discrimination between short and long survival (P = 0.04, log rank) for this threshold. DISCUSSION AND CONCLUSION: The proliferative tumor volume as determined by FLT–PET is associated with survival in high-grade malignant gliomas. SBR is the best method to estimate the PTV.

O.48. EARLY PROGRESSION BETWEEN SURGERY AND ADJUVANT CHEMO-RADIO THERAPY IN GLOBLASTOMA

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BACKGROUND AND PURPOSE: The assessment of early progression after surgery and before adjuvant treatment in glioblastoma (GBM) may (i)
offer the opportunity for customized target definition for radiotherapy, (ii) allow to modify the therapeutic program also by the patient enrollment into experimental trials, and (iii) permit to monitor more precisely the response to therapy. However, data on early progression in GBM are still lacking. Herein, the incidence and the methods to identify this phenomenon were investigated. MATERIALS AND METHODS: Thirty-seven patients with newly diagnosed GBM were retrospectively analyzed. Early post-operative magnetic resonance imaging (MRI) was compared with 1-mo postoperative examination to evaluate the extent of surgery and to identify possible new areas of contrast enhancement (CE). To classify these areas of CE as suggestive of tumor growth or surgical effect, 4 different magnetic resonance imaging (MRI) approaches were compared: (i) T2-EPMR diffusion, (ii) T2-weighted imaging, (iii) 1-mo diffusion, and (iv) 1-mo perfusion. RESULTS: Based on EPMR, 67% of cases were classified as incompletely resected. Seventeen out of 37 (46%) patients showed an increased area of CE between surgery and chemo-radiation. By EPMR diffusion, in 3 of 17 patients these new CE corresponded to induced diffusion and therefore indicated postoperative infection; in the other 14 of 17 patients, they were indicative of tumor progression or a combination of progression and infection. Comparing T2-weighted imaging EPMR vs 1-mo, 8 of 17 showed an increase of edema, suggestive of tumor progression. In the new areas of CE, by 1-mo diffusion, 2 of 17 patients showed the coexistence of reduced diffusion. Finally, by 1-mo perfusion, 11 of 17 patients showed the coexistence of hyper-perfusion. Considering EPMR diffusion and 1-mo perfusion, they provided the most similar classification with an agreement in 11 of 17 cases. It is noteworthy that the extent of resection does not seem to influence the rate of tumor progression: 33% of the patients that performed gross total surgery vs 40% of those partially resected, experienced disease progression. CBV and USNM findings suggested that early progression frequently occurs in GBM between surgery and the beginning of adjuvant treatment. EPMR diffusion, identifying post-surgical ischemic areas, and perfusion, detecting neo-angiogenesis, seemed to be more reliable approaches.

SUPPORTIVE CARE

O.49. IDENTIFYING CLINICAL DEPRESSION IN PATIENTS WITH BRAIN TUMORS
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BACKGROUND: Depression is under-recognized in patients with brain tumors. A standardized psychiatric interview is the “gold standard” method for diagnosing clinical depression, however the frequency of depressed and nondepressed glioma patients compared with a structured psychiatric interview. Major and non-major depressive disorders, excluding visual-spatial and some other. CONCLUSIONS: There is need of special educational and psycho-social programs for the children with recurrent brain tumors and their families.

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

O.51. A HADS DEPRESSION SUBSCALE SCORE ≥ 8 CAN HELP SCREEN FOR DEPRESSION IN ADULTS WITH PRIMARY GLIOMA
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BACKGROUND: No study has validated a screening tool for the purposes of diagnosing depression in adults with glioma. We examined whether the hospital anxiety and depression scale (HADS) discriminates between depressed and non-depressed glioma patients compared with a structured psychiatric interview. METHODS: This was a prospective, two-center, longitudinal cohort study of adults with newly diagnosed primary cerebral glioma. All subjects had a structured clinical interview to diagnose or exclude MDD. Data are presented from the first two time-points: T1 (shortly after starting radiotherapy, or equivalent) and T2 (3 months later). RESULTS: We examined 155 patients at T1 and 108 at T2. Fifty-seven percent patients were male. Mean age was 54 years, 86% had high-grade glioma, 78% received radical radiotherapy, and the median KPS was 90. We diagnosed MDD in 20 patients at T1 (12.9 ± 5.3%) and in 16 cases at T2 (14.8 ± 6.7%). Of the 20 patients with MDD at T1, 2 had recovered by T2; 7 continued to have MDD and 11 dropped out of the study. Nine new patients developed MDD by T2. These changes underlay the overall tendency for the point prevalence of MDD to increase over time (P = .065, McNemar test). We found univariate associations (all χ2, P < .05) between MDD and functional impairment (KPS ≤ 70), current steroid use, different grade of depression, marital satisfaction, current antidepressant prescription and/or high emotional distress (NCCN distress thermometer score ≥ 4/10). In multivariate analysis, MDD was independently associated with functional impairment and high emotional distress (logistic regression χ2, P < .001, R2 = .294). CONCLUSIONS: This is the first longitudinal study of depression in glioma patients using clinical interview. Major depression afflicted nearly 1 in 5 individuals during the study period. MDD persisted at reassessment after 3 months, and new cases occurred over time. Those with MDD were different in the longitudinal study. Functional impairment and emotional distress were independent risk factors. Clinicians should screen for depression in patients with glioma who report high distress on the NCCN distress thermometer, or who are prescribed antidepressants (KPS ≤ 70). They may also consider screening those with epilepsy, who are an easily identifiable group. The lack of association with any tumor-related variables suggests that in glioma, MDD could be more representative of a psychological reaction to loss than a “direct” tumor disruption of neuronal emotional networks. However, more research on this question would be required.
O.52. SCREENING FOR COGNITIVE IMPAIRMENT IN PRIMARY BRAIN TUMOR: IS THE MONTREAL COGNITIVE ASSESSMENT A MORE SENSITIVE TOOL THAN THE MINI MENTAL STATE EXAMINATION?

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BACKGROUND: The cognitive sequelae of primary brain tumor (PBT) and its associated treatments are well established. Although the mini mental state examination (MMSE) is widely used as a screening measure to detect cognitive impairment, it has limitations. This study aimed to compare a newer and potentially more sensitive screening tool, the Montreal Cognitive Assessment (MoCA), to the MMSE in a neuro-oncology population.

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

O.54. EPILEPSY AT THE END OF LIFE IN MALIGNANT GLIOMAS

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Epilepsy is common in patients with brain tumors. Frequently, an epilepsy sign is the central lesion, but temporal lobe epilepsy also may also occur. More than one-third of cases with primary brain tumors present with epileptic seizures, and the incidence at diagnosis varies with histological type and location. Another 10%–30% of patients develop epilepsy in the course of their disease. Patients who present with seizures at the first sign of a malignant glioma are at increased risk of recurrent seizures despite treatment with antiepileptic drugs. However, little is known about the incidence of epilepsy in the last stage of disease and at the end of life of brain tumor patients. We retrospectively analyzed the incidence of seizures in the last months of life in a series of patients affected by malignant gliomas assisted at home during all the course of disease until death with a comprehensive neuro-oncological home care program. One hundred fifty-seven patients affected by malignant gliomas were included in this study. Epilepsy at onset was present in 52 (33.1%) patients; 33 (21%) patients presented late onset epilepsy (during the course of disease and before the last months of life); 58 patients (37.6%) presented epilepsy in the last month before death. In 9 cases, seizures occurred in the last month of life in patients presenting previous epilepsy. The incidence of seizures in the last month of life was higher in patients presenting late onset epilepsy (25 of 33, 75.8%) with respect to the group of patients presenting early onset (25 of 52, 48.1%). In the group of patients not presenting previous epilepsy (72 of 137, 46.0%), the incidence of epilepsy at the end of life was 12%. In this group, 47 patients received anticonvulsant prophylactic treatment and 25 not. The occurrence of seizures was not correlated with anticonvulsant treatment. Anticonvulsant treatment at the end of life of brain tumor patients presents particular concerns with respect to other stages of disease, given the frequent difficulty to swallow oral therapy in patients dying. Oral treatment needs to be changed in advance with intramuscular or subcutaneous administrations. More studies should be addressed to the issue of epilepsy at the end of life in brain tumor patients.

O.53. HOW TO BEST MEET THE NEEDS OF PATIENTS WITH A Glioblastoma and their families: screening for psychosocial distress or a standard consultation with a social worker as part of their medical treatment?

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PURPOSE: The aim of the study was to evaluate the need of integrated psychosocial counseling as part of the treatment plan in patients with a high-grade glioma and to investigate whether standard counseling leads to improved psychosocial support for the patients and their family.

MATERIALS AND METHODS: Patients with a glioblastoma multiforme (GBM) are potentially faced with more physical, psychological, and social problems because of the nature of their illness. Patients are aware of the fact that they have an aggressive tumor with a limited lifespan. Owing to its effect on the cerebral function, not only the patient can experience a great loss of health and functioning, but the disease also has an obvious social impact on family life. The family often needs to take on new responsibilities and has to face at the same time the fear of losing their loved one. Since 2003, in MAASTRO clinic, all patients are screened on the level of psychosocial distress using a short validated screening inventory, the screening inventory of psychological problems (SIPP). Despite the resulting advice, not all patients make use of the psychosocial support. To improve psychosocial care, two strategies are followed: all patients are selected for counseling using the SIPP. Patients with a GBM are offered a counseling session with a social worker specialized in oncology as part of the treatment plan. The purpose of a standard counseling session is to check how the patient and his family are coping with the new situation (distress), to give psycho-education, emotional support, and practical advice and explain what the social worker can mean for them during and after treatment.

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

Glioma

O.55. INF-β SENSITIZES GLIOMA CELLS TO TEMOZOLOMIDE IN AN MGMT- AND P53-INDEPENDENT MANNER

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The alkylating agent temozolomide is the first drug to significantly prolong progression-free and overall survival when used in combination with surgery and radiotherapy in newly diagnosed glioblastoma. Glioma cell sensitivity to temozolomide is strongly associated with promoter methylation of the Oβ-methylguanine transferase (MGMT) gene. Further, in vitro studies
have demonstrated that the restoration of wild-type p53 activity also sensitizes glioma cells to temozolomide. On the basis of prior reports that demonstrate a sensitization of glioma cells to temozolomide by interferon-β (INF-β), we aimed at characterizing the underlying mechanisms in more depth. We report that human glioma cells uniformly express mRNA for interferon receptors I and II whereas only interferon receptor II protein is consistently detected by flow cytometry at the cell surface. INF-β strongly sensitizes glioma cells to temozolomide-induced reproductive cell death. This sensitization is independent of p53 as glioma cells with a siRNA-mediated silencing of the p53 gene become more susceptible to temozolomide after prior exposure to INF-β, too. Further, MGMT-negative glioma cells and transfectants genetically engineered to overexpress MGMT can be equally sensitized to temozolomide by INF-β. This effect of INF-β is observed in acute cytotoxicity assays and in clonogenic survival assays. Most importantly, there is also a sensitization of stem-like glioma cells to temozolomide by INF-β. In summary, we find that the INF-β-mediated sensitization to temozolomide is neither mediated by MGMT nor limited to MGMT-negative or -positive cell lines, suggesting that INF-β might be a powerful adjuvant to increase the benefit from temozolomide chemotherapy in glioblastoma.

O.58. NON-R132 MUTATIONS IN IDH IDENTIFY A NOVEL SUBGROUP OF LOW-GRADE GLIOMAS WITH DISTINCTIVE LOCATION, INFLTRATIVE BEHAVIOR, DISMAL OUTCOME, AND UNIQUE MOLECULAR PATHWAY

INTRODUCTION: Chromosomes 1p and 19q deletions and TP53 mutations represented the 2 main genetic alterations described in low-grade gliomas (LGGs). Interestingly, TP53 mutations and 1p19q codeletions were found to be exclusive. The predictive impact of these two genetic alterations on outcome in LGG is still source of controversies. However, LGGs harboring 1p19q deletion and no TP53 mutations have been reported to have a better prognosis than those with TP53 mutations or 1p36 and 19p deletions. Intriguingly, no data are available on the intermediate group of LGGs harboring a “null” phenotype (no TP53 mutation and no 1p19q codeletion).

Recently, mutations of succinate dehydrogenase enzyme isoforms 1 (IDH1) and 2 (IDH2) have been found in a large proportion of LGGs. To date, few data are available regarding the prognostic impact of IDH1 and 2 mutations in a homogenous LGG population. We address here, for the first time, a comprehensive analysis of the segregation of non-R132 mutations in IDH1 in distinct molecular subtypes of LGGs and report the clinical outcome and radiological features of this novel subgroup of tumors. METHODS: Patients (48) treated at Timone University Hospital, Marseille, France, between 2002 and 2008 were selected from the following criteria: histological diagnosis of WHO-grade II or III glioma; available para-necrotic and/or non-necrotic tissue; available magnetic resonance imaging data at diagnosis; clinical and follow-up data from the database; and written informed consent. The history of all tumors was centrally reviewed by two independent neuropathologists. Complete physical and neurologic examinations, KPS score, and MRI scan data were collected at the time of diagnosis. MRI data assessed by two neuroradiologists included tumor size, midline mass effect, heterogeneity, infiltration, contrast enhancement, and location. MRI-based extent of surgery was assessed at 3 months post-op. RESULTS: Sex ratio was 1.29 (27 men and 21 women) and median age 59.8 years (range, 22–71 years). A total of 41 mutations in IDH1 were identified (85.4%) and 2 mutations in IDH2. Five-year overall survival was 86.6% vs 60% in patients with R132 IDH1 and non-R132 IDH1 mutated tumors, respectively (P < .001). Furthermore, non-R132 IDH1–mutated tumors had a no mutation in TP53 and no codeletion of 1p19q in 71.4% of cases compared with 8.3% in non-R132 IDH1–mutated tumors (P < .001). Finally, 7 of 7 (100%) of the non-R132 IDH1–mutated tumors were paralimbic and displayed an infiltrative radiological phenotype compared with 9 of 41 (21.9%) patients of R132 IDH1–mutated tumors (P < .0001). CONCLUSION: Non-R132 mutations in IDH1 identify a novel subgroup of LGGs with distinctive topography, radiological aspect, and dismal outcome. Furthermore, non-R132 mutations in IDH segregate in a distinct molecular subtype of LGGs.

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

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

O.60. WHICH MOLECULAR SIGNATURES PREDICT PROGRESSION-FREE SURVIVAL AFTER SURGERY ALONE IN PATIENTS WITH LOW-GRADE GLIOMA?

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PURPOSE: TP53 mutations, 1p/19q codeletions, O6-methylguanine-
methyltransferase (MGMT) promoter methylation, and isocitrate dehydro-
genase (IDH)-1/2 mutations have been proposed to be associated with outcome in patients with low-grade gliomas. Here we sought to clarify whether these molecular signatures reflect a favorable natural course or a favorable response to radiotherapy or chemotherapy. Experimental Design: Ninety-three patients with diffuse astrocytoma WHO grade II (A-II, n = 27), oligoastrocytoma (OA-II, n = 24), or oligodendroglioma (O-II, n = 27), who had not received radiotherapy or chemotherapy after their first operation, were selected by a rigorous procedure before follow-up (n = 34) or until the first progression (n = 59), with a median follow-up of 6.1 years. Tumor tissues were analyzed for TP53 mutations, 1p/19q status, MGMT promoter methylation, and IDH-1/2 mutations. RESULTS: The estimated median progression-free survival (PFS) for patients with 1p/19q codeletion was 3.9 years (95% CI 2.9–4.9). Fifteen patients progressed and 17 patients died. The relative frequencies were 27.0% (24 of 89) for TP53 mutations, 41.1% (37 of 90) for 1p/19q codeletions, 43.8% (39 of 90) for MGMT promoter methylation, and 81.5% (75 of 92) for IDH-1/2 mutations. TP53 mutations were uncommon in patients with 1p/19q codeletions. None of the molecular markers was prognostic for PFS, using multivariable adjustment for histology, extent of resection, age, and gender. Similarly, none of the parameters predicted survival from first progression. Solely IDH-1/2 mutations were associated with prolonged overall survival. CONCLUSIONS: None of the studied parameters is a sen-
titive predictor of overall survival. CONCLUSIONS: None of the studied parameters is a sen-
titive predictor of overall survival.

O.61. A COMPREHENSIVE STUDY OF THE ASSOCIATION OF GENETIC VARIANTS OF A NEWLY DISCOVERED FAMILY OF GENES WITH BRAIN TUMOR RISK AND THEIR RELATIVES IN THE END-OF-LIFE PHASE


EGFR

O.60. WHICH MOLECULAR SIGNATURES PREDICT

PROGRESSION-FREE SURVIVAL AFTER SURGERY ALONE IN PATIENTS WITH LOW-GRADE GLIOMA?

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titive predictor of overall survival.

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

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

O.63. QUALITY OF LIFE IN HIGH-GRADE GLIOMA PATIENTS AND THEIR RELATIVES IN THE END-OF-LIFE PHASE

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

O.64. MALIGNANT GLIOMA PATIENT AND CAREGIVER CONGRUENCE IN QUALITY OF LIFE REPORTING

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BACKGROUND: Assessing quality of life (QOL) in patients with malignant gliomas (MGs) is often complicated by the progression of neurocognitive impairments that prevent patients to minimize their HRQOL. Accordingly, caregiver reports of a patient’s QOL are particularly valuable. The purpose of this study was to investigate QOL concordance between patient and caregiver, to identify relevant discrepancies. METHODS: Patients with MG within 6 months of diagnosis or relapse were eligible for this 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 magnetic resonance imaging (MRI) were done for tumor assessment and continued until tumor progression. Patients were asked to fill out the FACT-Br and their caregiver was asked to fill out the same questionnaire as they perceived the patient would respond. MRI was done approximately every 2 months and questionnaires were given prior to disclosure of MRI results. RESULTS: Seventy-two pairs of FACT-Br scales were collected over the course of the study from 25 patient–caregiver pairs. A consistent discrepancy between patient and caregiver was seen. Patients reported their overall QOL to be better than perceived by their caregivers by an average of 6.8 points on the 200-point scale (P = .01). This difference was observed similarly for patients with newly diagnosed and recurrent MG and their caregivers. Significant differences were found within sub-scales of physical (P = .03), emotional (P = .01), and functional (P = .02) well-being. Social well-being was the only subscale where a significant discrepancy was not noted. The average score for the FACT-General was 77.4 in this sample of MG patients, lower than the national average of 80+ across all ages. CONCLUSION: From the results indicated, patients consistently report their QOL to be more favorable than perceived by their caregivers. 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 for patients with MG.

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

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

O.66. Glioblastoma in Elderly Patients: Health-Related Quality of Life (HRQoL) in a Randomized Trial Comparing 6-Weeks vs Hypofractionated RT over 2 Weeks vs Temozolomide ChemoTherapy (TMZ)

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BACKGROUND: Despite advances in treatment, survival of patients with GBM over 60 years is still often less than 1 year. In the perspective of a short expected survival, the quality of the remaining life and the effects of therapy on health-related quality of life (HRQoL) should be given special emphasis when recommending treatment for the individual patient. Several studies have focused on survival of the elderly, but few data are available on HRQoL for different treatments. In a randomized trial, we compared survival and HRQoL for 3 treatment options, 6 weeks of RT, vs hypofractionated RT, or chemotherapy with TMZ. MATERIALS AND METHODS: Newly diagnosed GBM patients, age
patients. Deterioration and is associated with a prolonged survival in a subset of patients. In our series, the median overall survival was 10 months with 12 and 36 months survival proportions of 46% and 26%, respectively. Similar observations were noted for Group C. Painful neuropathy and symptomatic cranial nerve, and neural plexus infiltration occurred at a similar rate (40%–58%) in M0 patients. In the multivariate analysis, in the middle of radiotherapy, after 2 cycles of chemotherapy, and at 6 weeks, 3 months, and 6 months after start of treatment, HRQoL was significantly better in M0 patients. In 24 patients with paired preoperative and 2 cycles chemotherapy plasma samples, IgE levels increased after successful removal of the tumor (127.5 vs 62.3 weeks). We also collected longitudinal plasma samples from 70 patients with GBM and compared the plasma IgE levels before operation, 1 week after operation, in the middle of radiotherapy, after 2 cycles of chemotherapy, and after recurrence. We determined the correlation between plasma IgE levels and the outcomes of the patients. RESULTS: Plasma IgE levels correlate with the diagnosis and prognosis of glioma patients. BACKGROUND: Previous studies have shown that glioma patients report allergies less frequently, and have lower IgE levels than controls. To evaluate its potential as a surrogate biomarker for glioma, we measured plasma IgE levels in glioma patients and healthy controls, and correlated them with clinico-pathological factors and the patients’ outcome. METHODS: We used enzyme-linked immunosorbance assay (ELISA) to determine the plasma IgE levels of 25 normal subjects and 232 glioma patients. (85 grade II glioma patients, 40 grade III glioma patients, and 107 GBM patients). We also collected longitudinal plasma samples from 70 patients with GBM and compared the plasma IgE levels before operation, 1 week after operation, in the middle of radiotherapy, after 2 cycles of chemotherapy, and after recurrence. We determined the correlation between plasma IgE levels and the outcomes of the patients. RESULTS: Plasma IgE levels were significantly lower in glioma patients (P = .004). low-grade glioma patients have lower IgE levels than high-grade glioma patients (P = .029). Oligodendrogial tumors have higher IgE level than astrocytic tumors and mixed tumors both in grade II (P = .014) and grade III (P < .001) glioma patients. In 24 patients with paired preoperative and 2 cycles chemotherapy plasma samples, IgE levels increased after successful removal of the tumor (127.5 vs 62.3 weeks). 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INTRODUCTION: Glioblastoma (GBM) is a highly vascularized tumor, and endothelial cell proliferation is one of the neuropathologic hallmarks of the disease. Therefore, the concept of interfering with the generation of new blood vessels in GBM as a promising approach. However, agents such as bevacizumab have shown good response rates with bevacizumab, an antibody against vascular endothelial growth factor (VEGF). Yet, the effect is short lived and the physiologic mechanisms of bevacizumab action and the biologic consequences are poorly understood. MATERIAL AND METHODS: Here, we assessed the response to bevacizumab of highly angiogenic and invasive GBM xenografts, obtained by serial passaging of human GBM biopsies in nude rats. Animals with orthotopic tumors received weekly i.v. injections of 10 mg/kg bevacizumab for 3 weeks. Before sacrifice, animals were analyzed by magnetic resonance imaging (MRI) on a 7T Pharmascan (Bruker). MRI protocols included T1- and T2-weighted sequences to assess tumor morphology and edema, MR spectroscopy to assess key metabolite concentration, diffusion-weighted imaging to assess cellularity, and dynamic contrast enhancement MRI to assess tumor perfusion, and vascular permeability. After sacrifice, tumors were harvested for transcriptomic, proteomic, and metabolomic studies as well as histology and immunohistochemical analysis. RESULTS: In agreement with clinical data, we found that bevacizumab reduces vessel permeability and leakage of contrast. The treatment prolonged K trans and Vp parameters. Interestingly, bevacizumab reduced blood flow and blood volumes, while spectroscopy data point at increased lactate concentration in treated tumors. A reduction in vessel number was observed while the extent of cell infiltration in the tumor parenchyma was significantly increased. Key angiogenesis-related genes were upregulated after treatment. CONCLUSION: Bevacizumab treatment in GBM leads to a reduction of blood vessels and increased tumor hypoxia which is accompanied by increased cell invasion, a novel model of tumor cell plasticity involving a metabolic switch will be discussed.

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

CELL BIOLOGY AND SIGNALING

P.001
PROTEIN TYROSINE PHOSPHATASES IN GLIOMA BIOLOGY
A. C. Navis1, J. W. J. Jeuken1, J. T. G. Schepem1, B. Celda3, V. Esteve3, W. P. Leenders1, P. Wesseling1, and W. J. A. J. Hendriks2; 1Department of Cell Biology, Nijmegen Centre for Molecular Life Sciences, Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands; 2Department of Cell Biology, Nijmegen Centre for Molecular Life Sciences, Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands; 3Department of Physical Chemistry, University of Valencia, Valencia, Spain

Receptor tyrosine kinases (RTKs) such as EGFR, PDGFR, and MET are well known to have an important role in oncogenic signaling in gliomas. Phosphorylation of tyrosine residues on proteins through such RTKs can be counteracted by protein tyrosine phosphatases (PTPs). An important role for PTPs as “fly side of the coin” for RTK activity in glioma oncogenesis is therefore to be expected. Although the PTP PTEN is clearly functioning as a tumor suppressor in high-grade gliomas, the role of other PTPs is still largely unknown. To elucidate the relevance of PTPs in glioma biology, we first performed an in depth literature search that yielded information on 107 PTP genes present in the human genome to be potentially implicated in glioma biology. Besides PTEN, overexpression of PTPRZ is clearly associated with these tumors, although its exact function in oncogenesis is not clear at present. Also inactivating mutations, including...
homogenous microdeletions, in PTPRD. Resistance to cetuximab, which is present in most patients, is often associated with somatic mutations in the epidermal growth factor receptor (EGFR) gene. To identify anti-cancer targets in GBM, we performed genomic sequencing of 125 glioblastoma samples, 82 of which harbored mutations in the EGFR gene.

RESULTS: A total of 262 somatic mutations were detected in the EGFR gene, of which 223 (85%) were present in only one sample. We identified 18 novel somatic point mutations in EGFR and 35 novel coding EGFR mutations that were previously unreported.

CONCLUSION: These findings provide new insights into the molecular heterogeneity of glioblastoma and identify novel somatic mutations in the EGFR gene that may be potential targets for therapy.

P.002*. DOWNREGULATION OF MEMBRANE PROTEIN UROKINASE-TYPE PLASMINOGEN ACTIVATOR RECEPTOR ASSOCIATED PROTEIN MAKES GLIOMA CELLS IMMOBILE AND CAN BE A TARGET FOR NOVEL GLIOMA THERAPY

S. Takahashi, *T. Kawase, and M. Toda; Keio University, Tokyo, Japan

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

P.003*. METABOLIC CHARACTERIZATION OF STEM-LIKE GliOMA STA 2 CEL LINES

S. C. Dietz 1, J. Grifiths 1, and C. Watts 1; 1Cambridge Research Institute, CRUK, Cambridge, UK; 2Centre for Brain Repair, Cambridge, UK

INTRODUCTION: The biology of glioblastoma multiforme (GBM) is poorly understood, but there is currently great interest in the metabolic make-up of this cancer type. METHODS: Cell lines derived from human GBM tissue were cultured under serum-free conditions following the Cambridge Protocol, which enriches the culture with tumor competent, self-renewing cells. We used 1H-NMR to analyze the concentrations of metabolites in cell extracts and cell media for 4 cell lines. RESULTS: Using principal component analysis, it was possible to determine the differences between the metabolic profiles of the 4 cell lines tested, and to detect significant changes in their metabolic profile after cell differentiation. Most of the metabolic changes contributing to these changes have now been identified. Further data mining by carbon flux analysis, which quantifies the changes, shows that they are consistent between all 4 cell lines.

CONCLUSION: Our data suggest that myo-inositol, which is present in the stem-like state, is reduced to undetectable levels by differentiation. Also several amino acids show different secretion and consumption patterns in the differentiated state compared with the initial stem-like state.

P.004*. REVERSAL OF EFFECT OF U87 DERIVED MICRO-VESELICES ON BIOLOGICAL PROCESSES OF GliOMA ST Ai FORME MULTI FORME

M. I. Broekman 2,5, S. N. L. N. Maa 1, S. J. Skeg 1, X. O. Breakefield 1, and M. Sena Esteves 2; 1Department of Neurosurgery, University Medical Center Utrecht; Utrecht, Utrecht, Netherlands; 2Neuro-oncology Laboratory, Department of Neurosurgery, Erasmus Medical Center, Rotterdam, Netherlands; 3Department of Neurology and Gene Therapy, University of Massachusetts Medical School, Worcester, MA; 4Molecular Neurogenetics, Department of Neurology, Massachusetts General Hospital, Charlestown, MA

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

P.005*. TARGETING THE RELAPSE-INDUCING CELL POPULATION OF GliOMA ST Ai FORME

M. Glas 1, 2, B. Rath 1, M. Simon 1, R. Reinartz 2, A. Schramme 2, D. Tragerer 2, A. Leibnitz 2, H. Schiel 2, M. Simon 3, O. Brustle 2, B. Steinfarz 2, T. Petesch 2, D. A. Steindler 2, J. Schramm 3, R. Reinartz 2, A. Schramme 2, D. Tragerer 2, B. Steinfarz 2, T. Petesch 2, D. A. Steindler 2, J. Schramm 3, O. Brustle 2, B. Steinfarz 2, T. Petesch 2, D. A. Steindler 2, J. Schramm 3, O. Brustle 2

OBJECTIVE: Residual glioblastoma (GBM) cells that persist in the surrounding parenchyma after complete macroscopic resection represent one of the major driving forces of mortality in GBM. While exposure to postsurvival therapy, little is known on their biology. It was the goal of this study to isolate and profile these potentially relapse-inducing cells. METHODS: Paired tissue specimens were obtained from 33 GBM patients. Residual GBM cells were derived from experimental biopsy of the resection margin after completion of standard neurosurgery. A second tissue sample, used as an internal reference, represented the routinely resected tumor core. Tumor cells were isolated, expanded under controlled in vitro conditions, and profiled (histology, growth kinetics, invasion studies, self-renewal analysis, qPCR, combined SNP/FISH analysis, FACS, in vitro drug–response assays, and xenotransplantation) in direct comparison. RESULTS: Sample analysis revealed residual cells as distinct malignant subentities in GBM. They fulfill the functional criteria of (rapidly proliferating, highly invasive) transit amplifiers rather than to represent (multipotent, self-renewing) stem cells. Stem-like GBM cells were almost exclusively detected in the routinely resected tumor core (71% of the center vs 14% of the periphery). Expression analysis revealed in 52 of 72 comparative measures, that cellular levels of PDGF-R/A, TGF-β-2, TGF-β-1, VEGF-2, VEGF-D, and/or PTPA transcripts varied more than 50% between core and residual cells of the same GBM patient. Also, in 16 of 25 comparative measurements, different in vitro responses to radio- and/or chemotherapy (CCNU, Temozolomide) were noted. We found that tumor cells are represented by the four subentities of GBM tumor cells, and that the neo-clonal resection margin regions to closely assess the degree of intragroup heterogeneity. These experiments similarly revealed residual cells as clearly distinguishable from GBM core cells in every patient investigated (n = 5). Ongoing studies focus on the isolation and characterization of residual tumor cells as well as on the potential use of these cells as an in vitro model system for drug screening. CONCLUSION: Residual cells are unique cellular targets in GBM. They could be responsible for the recurrence of disease. Thus, characterization of residual tumor cells in the preoperative setting may open new avenues for future diagnosis and treatment of GBM.

This study was supported by BONFOR* and VW Foundation .

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P.006. CARBON ION RADIATION WITH OR WITHOUT THE ADDITION OF CILENITIDE IS AN EFFECTIVE INHIBITOR OF INTEGRINE-MEDIATED TUMOR CELL MIGRATION S. Reken1, D. Habermehl1, L. Würth2, A. Mohr3, K. Lindel3, K. Weber4, T. Kromer5, T. Kromer5, 1Department of Radiation Oncology, Heidelberg, Germany; 2HIT – Heidelberger Iontherapie-Zentrum, Heidelberg, Germany

BACKGROUND: Multiple extracellular matrix proteins have been described to promote glioneuronal cell motility accounting for infiltrative growth. Fibronectin (Fn) and vitronectin (Vn) have recently been targeted by cilenitide (CGT), a cyclic peptide known to inhibit αvβ3 and αvβ5 integrins that interact with Vn (αvβ3/β3) and Fn (αvβ5/β5). In most glioma, untreated tumor cells, radiotherapy or chemotherapy alone shows no efficacy and it was also shown to alter cell migration. We recently demonstrated that photon irradiation enhances tumor cell migration at low doses, thus, possibly promoting tumor cell infiltration into the adjacent healthy brain. In the present study, we analyzed the effects of carbon ion irradiation on glioma cell migration ± the addition of CGT. METHODS: Twenty-four hours before migration experiments and FACS analyses, U87 glioma cells were irradiated with single photon doses of 1, 2, and 10 Gy using 6 MV photons at a linear accelerator. Particle radiotherapy was applied with an extended Bragg peak (E = [128 ± 7] MeV/n, LET = (91.5 ± 1.5) keV/µm) at single carbon ion doses of 0.5 and 3 Gy at the Heidelberg Ion Therapy Center (HIT). The migration chambers were separated by 8-µm pore size polycarbonate membranes coated with Fn and Vn. Cells were then plated on the upperwell. After 24 h, cells that migrated through the porous membranes were stained and analyzed microscopically by an investigator blinded to experimental setup. Quantitative FACS analysis of integrin expression was performed with a BD FACScan using PE- and FITC-labeled antibodies directed against αv and β3, respectively. αvβ5 and β3 expression of U87 cells was not altered by CGT. In migration assays, CGT inhibited transmigration through Vn- but not Fn-coated membranes. Photon irradiation increased migration on both Fn and Vn at low doses of 2 Gy. Addition of CGT to photon-irradiated cells decreased transmigration through Vn- but not Fn-coated membranes. FACS analyses revealed an increased expression of αvβ3 and αvβ5 following low-dose photon irradiation, which was still detected after single doses of 10 Gy. On the contrary, carbon ion irradiation alone significantly inhibited both Vn- and Fn-based transmigration and fully abrogated any migration if combined with CGT. Accordingly, expression of αvβ3 and αvβ5 decreased following carbon ion doses of 0.5 and 3.0 Gy. CONCLUSION: Low doses of photons, such as applied in fractionated RT, bear the risk of promoting glioma cell migration on Vn and Fn, whereas CN may additionally be administered to counteract photon-induced hypermigration toward Vn; however, Fn-based migration is not affected by CGT. Carbon ion irradiation achieves strong inhibition of migration on both Vn and Fn, which is further increased by combination with CGT. Therefore, local infiltration of glioma cells may be prevented efficiently by using carbon ion RT in regimes combined with molecular targeted therapies.

P.007. IGF/IGFBP SIGNALING IN MERLIN-DEFICIENT TUMORS C. O. Hanemann, S. Ammoun, M. C. Schmid, N. Ristic, E. Ercolano, and L. Zhou; Peninsula Medical School, Plymouth, UK

All schwannomas, 50%–60% of meningiomas, 29%–38% of ependymomas, and all tumors as part of the inherited tumors disease. Neurofibromatosis 2 (NF2) are caused by loss of merlin. Current therapies for merlin-deficient tumors especially in NF2 are insufficient, leaving patients with severe morbidity. There is a need for new therapies. We focused on schwannomas as they are a hallmark of NF2 and serve as serve as a model for merlin-deficient tumors. We aim to define therapeutic targets for schwanna treatment. Using our in vitro model for human schwannoma, we showed the overexpression/activation of platelet-derived growth factor receptor α (PDGFRα) and ErbB2/3 in primary schwannoma. Enhanced activation of extra-cellular signal-regulated kinase 1/2 (ERK1/2) and AKT and increased proliferation which we successfully inhibited by Sorafenib, AZD6244, and Lapatinib. Basal proliferation was partly dependent on PDGFRα and ErbB2/3. Activity on ERK1/2 and ErbB2/3. Increased adhesion of schwannoma was also PDGFRβ-dependent. These data suggest the involvement of additional factors. We have in this study investigated insulin-like-growth-factors-I/II (IGF-I/II) as they are important for Schwann cells, regulate adhesion, proliferation, and survival. IGFR receptor is also overexpressed and activated in schwannoma cells. We suggest that IGF/IGFBP system is involved in schwannoma development. Targeting IGF/IGFBP system together with PDGFR-β and possibly ErbB2/3 pathways would be an excellent approach in schwannoma treatment. We show dissection of respective pathways that seem crucial for any educated drug therapy being it mono or combinational therapy.

P.008. DOES BIPARTITE CLUSTER OF 7 + 46 MICORNAS ON CHROMOSOME 14q32.31 PLAY A ROLE IN GLIOMAGENESIS? L. Lavon, A. Granit, O. Einstein, and T. Siegal; Hadassah Hebrew University Medical Center, Jerusalem, Israel

BACKGROUND: We demonstrated that glions exhibit a microRNA (miRNA) expression profile that is reminiscent of neural precursor cells (NPCs) (Lavon et al. Neuro-Oncology, 2010). There are obvious similarities in the self-renewal capacity of stem cells and cancer cells but the tumorigenic role of miRNAs that display similar expression profile in glions and nontransformed NPCs have not been established yet. The bipartite cluster of 7 + 46 miRNAs on chromosome 14q32.31 was uniformly downregulated in all glions tissues as well as in NPCs. This region is frequently deleted or, genetically altered in gliomas and in other hematopoietic and solid malignancies. Therefore, we assumed that it might represent a large tumor suppressor miRNA cluster. OBJECTIVE: To study the function of individual miRNAs from the 14q32.31 cluster. METHODS: To evaluate the role of the investigated miRNAs, we cloned the pri-microRNA into a lentivirus-based vector under the control of CMV promoter. This vector is co-expressing green fluorescent protein as a reporter gene, permitting tracking of infected glioma cells. U87 MG glioma cell line was transduced with either a lentivirus-based vector that contains one of the miRNAs on 14q32.31 or with an empty vector. Expression of the mature miRNAs was evaluated by real-time RT PCR. The effect of each miRNA on cell proliferation was tested by cell titration assay. RESULTS: Expression of individual miRNAs from the miRNA cluster on chromosome 14q32.31 was achieved by retroviral infection of U87 MG glioma cell line. Overexpression of 14q32.31 miR1 reduced the proliferation rate of the U87 MG cell line in a dose-dependent manner. Overexpression of 2 of the tested miRNAs (14q32.31R1 and 14q32.31R2) induced spheroid-like cell morphology. CONCLUSIONS: miRNAs members derived from the miRNA cluster in chromosome 14q32.31 might play a role in the proliferation rate and morphology of gliomas. Further investigation is currently ongoing to uncover the role of these miRNAs on invasion, soft agar colony formation, and apoptosis is currently tested in vitro and their effect on tumorigenicity is investigated in vivo.

P.009. BIM MEDIATES GEFITINIB-INDUCED APOPTOSIS IN GLIOMA CELL LINES EXPRESSING WILD-TYPE EGFR A. García-Claver, E. Pérez-Máñan, Y. Ruano, G. Pérez-Díaz, A. González, M. Mollejo, A. Rodríguez de Lope, B. Meléndez, and Y. Campos-Martín; Hospital Virgen de la Salud, Toledo, Spain

BACKGROUND: Tyrosine kinase inhibitors (TKIs), as gefitinib, are currently used for the treatment of human tumors, including malignant glioma as a second-line treatment. Previous studies in lung cancer have observed that, a pro-apoptotic protein from the Bcl2 family, is involved in the apoptotic effect of TKIs. They also propose that either inhibition in the PI3K/Akt pathway or MEK/Akt pathway causes an increase in Bim levels. In this study, we analyze the apoptotic effects of gefitinib treatment and Bim expression in glioma cell lines. MATERIAL AND METHODS: Seven glioma cell lines (U118, SW1088, A172, SW173, G03S, SF767, and T98G) were treated for 48 hours with 10 µM of gefitinib or with solvent DMSO alone in a serum-free medium with 100 ng/mL of EGF. Apoptosis was assayed by flow cytometric analysis by Annexin V–FITC staining. Protein expression of Bim, p-Akt, p-Erk, and tubuline were performed by Western blot (WB) using total protein lisates from cell cultures. For WB, before collecting, cells were treated for 15 minutes with 50 ng/mL of EGF to activate the EGFR pathway. Detection was performed with IRDye680/800CW-conjugated secondary antibodies and quantification of proteins bands was carried out with Odyssey (Lilor Bioscience) software. Bim gene copy number (BCL2L11) was analyzed by Multiplex Ligation-dependent Probe Amplification Sequencing analysis of exons 18–21 of EGFRT were done. RESULTS: None of the 7 cell lines showed EGFRT mutation in exons 18–21 and none of them showed deletions or gain. Two of the 7 cell lines (SF767, U118) suffered apoptosis after treatment with gefitinib. These cell lines showed a decrease in Akt and Erk phosphorylation as well as an increase in Bim expression after treatment. Among the 5 cell lines that did not suffer apoptosis, 2 of them (GOS3 and SW1088) showed a reduction in p-Akt and an increase in Bim expression after gefitinib treatment. A decreased level of p-Erk in the other 3 cell lines.
might be crucial for glioma migration and possibly invasion. New panel of interactions between lactate metabolism and TGF-
that TGF-
RNA by RNA stabilization. Together with our recent results that show from several human cancers. Recent paper showed that LDH-A is able to
of LDH-A has been found in aerobic glycolysis, a mechanism well known
We demonstrate, for the first time, that knockdown of LDH-A can decrease
leads to a decreased migration of high-grade glioma cells. DISCUSSION: In supernatants of siLDH-A–treated cells. In migration assays, siLDH-A
and protein level. THBS-1 leads to an increased level of activated TGF-
high-grade glioma and decreases the expression of THBS-1 on the RNA
Chamber and scratch assays. RESULTS: siLDH-A suppresses TGF-
transfected cells were investigated using microarrays, RT-PCR, Western blot,
ent transfection of glioma cells with small interfering RNA directed against
Thrombospondin1 (THBS-1) is an extracellular protein important for acti-
remodeling the extracellular matrix (ECM) and inducing proteinases. (TGF-
glia
alternative mechanisms would be necessary to induce apoptosis.
Expression levels of TGF-
activation and processing of TGF-
activation of Bim itself cannot induce apoptosis in glioma cell lines, suggesting
that this chromosomal region is frequently deleted or genetically altered in both haematopoietic and systemic solid tumors. In a preliminary small scale
survey, we found a low rate of loss of heterozygosity (LOH) in this chromosomal region of only 5% in oligodendrogliomas and 35% in glioblastomas. The aim of this study was to verify the incidence of LOH in chromosome 14q32.31 and whether it might carry a potentially meaningful explanation for the previously observed downregulation of 7 + 46 bipartite microRNA cluster in gliomas. In addition, we examine whether there is any relationship between 14q32.31 LOH and other known prognostic markers, namely 1p, 19q, and 10q, and the methylation status of the promoters of MGMT and Pten genes. METHODS: A microsatellite analysis was performed on DNA that was extracted from paraffin-embedded samples of 95 gliomas. LOH of 14q32.31 is evaluated by using D14S65 at 14q32.2 and D14s252 at 14q32.31 markers. The analysis includes 39 oligodendrogliotal tumors (54% WHO grade II) and 55 astrocytomas (45% WHO grade III and IV). The final data analysis and the correlation between 14q32.31 LOH and other markers will be presented at the conference.

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

**P.012. INCIDENCE OF LOSS OF HETEROZYGOSITY IN CHROMOSOMAL REGION 14Q32.31 WHICH CONTAINS THE LARGE 7 + 46 BITAPRITE MICRONRNA CLUSTER, AND ITS RELATIONSHIP TO OTHER MOLECULAR MARKERS IN 95 GLIOMAS**

I. Lavon, R. Zelikovitch, A. Granit, A. Lokiec, E. Shalom, and T. Siegal; Hadassah Hebrew University Medical Center, Jerusalem, Israel

BACKGROUND: We demonstrated that the large 7 + 46 bipartite Dlk1-Dio3 microRNA cluster on chromosome 14q32.31 is uniformly downregulated in gliomas, embryonic stem cells, and neural progenitor cells. It might suggest that this cluster probably represents the largest tumor-suppressor microRNA cluster. Because there are only few microRNAs that are expressed only from the maternally inherited allele, deletion of the active allele may result in complete silencing of these microRNAs. There is strong evidence that this chromosomal region is frequently deleted or genetically altered in both haematopoietic and systemic solid tumors. In a preliminary small scale survey, we found a low rate of loss of heterozygosity (LOH) in this chromosomal region of only 5% in oligodendrogliomas and 35% in glioblastomas. The aim of this study was to verify the incidence of LOH in chromosome 14q32.31 and whether it might carry a potentially meaningful explanation for the previously observed downregulation of 7 + 46 bipartite microRNA cluster in gliomas. In addition, we examine whether there is any relationship between 14q32.31 LOH and other known prognostic markers, namely 1p, 19q, and 10q, and the methylation status of the promoters of MGMT and Pten genes. METHODS: A microsatellite analysis was performed on DNA that was extracted from paraffin-embedded samples of 95 gliomas. LOH of 14q32.31 is evaluated by using D14S65 at 14q32.2 and D14s252 at 14q32.31 markers. The analysis includes 39 oligodendrogliotal tumors (54% WHO grade II) and 55 astrocytomas (45% WHO grade III and IV). The final data analysis and the correlation between 14q32.31 LOH and other markers will be presented at the conference.

Standard treatment of glioblastoma multiforme (GBM) consists of surgery, radiotherapy, and temozolomide (TMZ). Clinical data show that GBMs with wild-type methyl-guanine methyl-transferase (MGMT) gene, which express the MGMT DNA repair protein, are resistant to TMZ. The PI3K/Akt “survival” pathway, which is activated in the majority of GBMs, is a main determinant of radioresistance. Activation of the pathway is mediated by the tumor suppressor gene Pten and by EGFR. The HIV protease inhibitor nelfinavir (NFV) has been identified as downregulator of this pathway via inhibition of its key protein Akt. Our studies focus on the interaction between irradiation, TMZ, and NFV in human established and long-term primary glialoma cell lines with known genetic profile with regard to Pten, EGFR, and MGMT. Cell lines were tested on expression of the MGMT protein and on key proteins of the PI3K/Akt pathway. Cell survival was determined by clonogenic assay. A clear correlation was found between the sensitivity of glioma cells to TMZ, both with expression of the MGMT repair protein and with MGMT gene promoter methylation. Enhancement of the radiation response by TMZ was noticed in 3 of 5 MGMT promoter methylated, TMZ-sensitive cell lines. Treatment of D384 cells (methylated MGMT; wtPten) with NFV alone for 24 hours decreased cell proliferation and was cytotoxic at doses exceeding 30 μM. Pretreatment with 20 μM NFV for 24 hours enhanced the radiation response. The data indicate that a targeted interference with disturbed molecular pathways in GBM is a promising approach to circumvent resistance to current therapies.
of these processes. We have demonstrated previously that the simultaneous downregulation of uPAR and uPA causes the activation of the extrinsic apoptotic pathway involving the mitochondrial Δψ collapse. From Western blot analysis of nuclear extracts from glioma cells (SNB19, U87) and xenografts (4910, 5310), we observed that uPAR is localized in the nucleus of these cells. Further analysis by immunoprecipitation, immunohistochemistry and transcription factor array revealed that uPAR strongly associated with EGR-2 among other nuclear molecules. As determined by Western blot analysis of cytoplasmic extracts, RNAi-mediated downregulation of uPAR caused the activation of BAK expression and release of cytochrome c into the cytoplasm in SNB19, U87, and 4910 cells, and to a lesser extent, in 5310 cells. Downregulation of both uPAR and BAK retarded mitochondrial Δψ collapse from Mito-PT staining, and Western blot analysis of cytochrome c release when compared with cells downregulated for uPAR alone. To determine whether uPAR binding to EGR-2 involved genetic material, we performed CHIP analysis by immunoprecipitating uPAR and PCR amplification of EGR-2−binding sequences. From the CHIP analysis, we observed that uPAR and EGR-2 form a complex with DNA in SNB19, U87, and 4910 cells, but form weak complexes in 5310 cells. Taken together, our results indicate the involvement of uPAR as a regulatory element with potential therapeutic implications.

P.015. ABRUPT HYPERMETHYLATION OF NON-PROMOTER ZYGOTE ARREST 1 (ZAR1) IN HUMAN BRAIN TUMORS

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Zygote arrest 1 (ZAR1) is a novel maternal-effect gene that plays crucial roles during the oocyte-to-embryo transition. Comprehensive methylation analysis of tumor-specific differentially methylated regions in human malignant melanoma has recently led to the identification of nonpromoter hypermethylation of the ZAR1 gene that has never been previously linked to aberrant methylated DNA. Notably, ZAR1 hypermethylation was frequently observed in melanomas but was absent in benign nevi, and ZAR1 expression was found to be upregulated in methylated tumors. We searched for nonpromoter ZAR1 hypermethylation in 90 primary human brain tumor samples, normal brain tissue from 1 autopsy case, and 7 glioma cell lines, employing Sequenom MassARRAY, in which bisulfite-treated fragments are quantitatively detected using time-of-flight mass spectroscopy. We also evaluated the ZAR1 transcript expression levels by quantitative real-time reverse transcription–PCR in 7 glioma cell lines. Hypermethylation of ZAR1 was frequently found in diffuse astrocytomas (7 of 7; 100%), anaplastic astrocytomas (16 of 17; 94%), glioblastomas (27 of 29; 93%), oligodendrogliomas (3 of 3; 100%), anaplastic oligodendrogliomas (3 of 3; 100%), and pituitary adenomas (9 of 10; 90%), but not at all in 3 pilocytic astrocytomas. Other tumor types showed infrequent hypermethylation of ZAR1, including meningiomas (12 of 27; 44%), oligoastrocytomas (4 of 4; 100%), medulloblastomas (2 of 2; 100%), and pituitary adenomas (9 of 10; 90%).

Diffuse infiltrating WHO grade II gliomas are relatively rare tumors. They account for 10%–15% of all gliomas with an incidence rate of 1 in 100,000 person-years, approximately. Epidemiological data are very rare, even exceptional. The aim of the present study was to estimate, with this preliminary work, the French national geographic distribution of all the histological cases of WHO grade II gliomas during a 4-year period. METHODS: The French Brain Tumor Database (FBTDB) witch is the biggest database concerning primary central nervous system tumors (PCNST) in Europe. This database continues to record all PCNST in France for which histological diagnosis is available. One of the major aims of this structure is to allow the realization of epidemiological studies. The methodology used for the geographic distribution analysis was simple: (i) identification of all the histological cases of glioma diagnosed between January 1, 2006 and December 31, 2009; (ii) for each glioma WHO grade II, number of cases, collection of the personal address (postal code) of the patient at the moment of the surgical procedure; and (iii) description of the geographic distribution of all cases in the French territory with the search of spatial clusters. RESULTS: We analyze at present intrastatal distribution of 6663 gliomas cases, 1000 from Alsace, 1000 from Champagne/Ardennes, 500 from Franche-Conté, 1000 from Languedoc Roussillon, and 1000 from Lorraine) corresponding to a population of 11 million of inhabitants. Preliminary results seem to show an important intraregional heterogeneity. The analysis at a national level is in progress. CONCLUSION: This original study aims to describe the geographic distribution of the WHO grade II gliomas at the level of the French territory. We will present the preliminary results concerning a population of approximately 11 millions of inhabitants.

P.017. WHO GRADE II GLOBLASTOMA DISTRIBUTION ON THE FRENCH TERRITORY: PRELIMINARY DETAILED RESULTS CONCERNING 6 REGIONS (ALSACE, BOURGOGNE, CHAMPAGNE/ARDENNES, FRANCHE, CONTE, LANGUEDOC ROUSSILLON, AND LORRAINE)

A. Darlik 1, S. Zouaoui 2, S. Aberkane 1, V. Rigas 1, H. Mathieu Daude 2, B. Tretarme 2, H. Duffaut 1, L. Baudet 2, and L. Taillandier 2; 1Unité de neurooncologie, Service de Neurologie, Hopital central, Nancy, France; 2French Brain Tumor Database (FBTDB). RESULTS: We anlyze at present epidemiological data are very rare, even exceptional. The aim of the present study was to estimate, with this preliminary work, the French national geographic distribution of all the histological cases of WHO grade II gliomas during a 4-year period. METHODS: The French Brain Tumor Database (FBTDB) witch is the biggest database concerning primary central nervous system tumors (PCNST) in Europe. This database continues to record all PCNST in France for which histological diagnosis is available. One of the major aims of this structure is to allow the realization of epidemiological studies. The methodology used for the geographic distribution analysis was simple: (i) identification of all the histological cases of glioma diagnosed between January 1, 2006 and December 31, 2009; (ii) for each glioma WHO grade II, number of cases, collection of the personal address (postal code) of the patient at the moment of the surgical procedure; and (iii) description of the geographic distribution of all cases in the French territory with the search of spatial clusters. RESULTS: We analyze at present intrastatal distribution of 6663 gliomas cases, 1000 from Alsace, 1000 from Champagne/Ardennes, 500 from Franche-Conté, 1000 from Languedoc Roussillon, and 1000 from Lorraine) corresponding to a population of 11 million of inhabitants. Preliminary results seem to show an important intraregional heterogeneity. The analysis at a national level is in progress. CONCLUSION: This original study aims to describe the geographic distribution of the WHO grade II gliomas at the level of the French territory. We will present the preliminary results concerning a population of approximately 11 millions of inhabitants.

P.016. “ON-CALL” REFERRAL PATTERNS OF PATIENTS WITH BRAIN TUMORS IN TWO NEUROSURGICAL CENTERS: USING DATA TO ORGANIZE SERVICES

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

P.018. INCREASED SURVIVAL IN Glioblastoma, A POPULATION-BASED STUDY BY THE AUSTRIAN BRAIN TUMOR REGISTRY

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BACKGROUND: Historically, median survival times of glioblastoma (GBM) patients ranged from 6 to 9 months. The analysis at a national level is in progress. CONCLUSION: This original study aims to describe the geographic distribution of the WHO grade II gliomas at the level of the French territory. We will present the preliminary results concerning a population of approximately 11 millions of inhabitants.
QUALITY OF LIFE

P.020*. SUPPORTING PATIENTS WITH A DIAGNOSIS OF MALIGNANT GLIOMA: THE ROLE OF THE NEURO-ONCOLOGY NURSE SPECIALIST
M. Stauss, J. Micker, V. McCready, G. Hendry, and P. Kane; Department of Neurosurgery, James Cook University Hospital, Middlesbrough, UK

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

P.019. NEOPLASTIC DIAGNOSIS TIMING PROFILE IN VON HIPPEL–LINDAU’S DISEASE: A PERSONAL SERIES EVALUATION
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INTRODUCTION: Von Hippel–Lindau’s (VHL) disease is a rare autosomal-dominant genetic disease, with a prevalence close to 1 in 40,000 inhabitants. The affected patients present nervous system and retinal hemangioblastomas (HGBs) and associated among others with paragangliomas/pheochromocytomas (PGL), endolymphatic sac tumors (ELST), and renal cell carcinoma (RCC). The object of this study is to evaluate the presenting timing profile of these tumors in a series of affected patients. MATERIALS AND METHODS: Age and sequence of imaging confirmed diagnosis of intracranial HGBs, PGLs, ELSTs, RCCs, evaluated in a series of 54 affected patients with a total amount of 245 diagnosed tumors, from 30 families studied and followed in a neurological familial neoplastic syndrome referral center, based in a neurosurgical unit. The patient’s clinical data are compared within the obtained clinical groups. RESULTS: One hundred thirteen intracranial, 33 spinal, and 44 retinal HGBs were diagnosed. Retinal HGB diagnosis was more precocious, with initial diagnosis at 8 years of age, and a median at 28. Intracranial HGBs are first diagnosed at 8 with a median at 34 years of age. Spinal HGBs have a later diagnosis, beginning at 9 years of age, with a median at 37. PGLs diagnosis began at age 11, with a median diagnosis at 33. ELSTs began at 23 years, with a median of age of 37. RCC was the latest performed diagnosis, starting at 20 years with a median at 39 years. Three disease molecule–confirmed carrier patients have not developed tumors yet. Five patients have died as a result of their HGB, at age 30–60 years old, and 2 more from RCC, some later. No relation has been observed between age of presentation and other clinical or molecular characteristics. CONCLUSIONS: In von Hippel–Lindau’s disease, the neoplastic occurrence begins at early age. Tumors are diagnosed in 20% of affected patients before age 19. A precocious diagnosis does not predict a more aggressive clinical course in relation to other clinical signs. On the other hand, the clinical temporal profile is not predictable with the molecular diagnosis. Deaths before 60 in these patients are commonly related to hemangioblastoma. A molecular diagnosis should be provided to all first-degree relatives of affected patients at an early age, so that clinical and imaging studies can be performed accurately following population, in order to obtain an early diagnosis and adequate management of these neoplasms.
Patients were evaluated before surgery, immediately after surgery, and 3 months after surgery. We have developed an extensive neuropsychological battery that allows a careful evaluation of patients and their well-being. Two hundred patients with high- and low-grade gliomas in the institutional database were included in this study. The neuropsychological battery that allows a careful evaluation of patients and their well-being. Two hundred patients with high- and low-grade gliomas in the institutional database were included in this study. The preoperative language disturbances are at-risk for more persistent aphasic disturbances; therefore, more insight into this subject is profitable. This study was conducted to investigate the spontaneous speech of older patients with LGGs in eloquent areas. METHOD: Thirty-four patients (22 males, 12 females) were included, and 21 healthy controls (8 males, 13 females) matched for age and education. Spontaneous speech from LGG patients was collected for analysis and served as an interview setting before awake craniotomy. The preliminary analysis shows that (i) only approximately 40% of the patients resumed a professional activity, (ii) the quality of life is altered, and (iii) despite the heterogeneity of the assessments, neuropsychological modifications seem mainly to concern attention and memory processes. CONCLUSION: As for the pediatric population, medulloblastoma adult survivors seem to present a late toxicity of the treatment. It justifies a discussion about the adaptation of the treatment modalities at least for the standard risk patients.

INTRODUCTION: Although it is already known that language deficits could occur in patients with LGGs, no previous studies are reported with respect to a detailed analysis of spontaneous speech. It must be noted that spontaneous speech is the most natural form of linguistic behavior. Patients with preoperative language disturbances are at-risk for more persistent aphasic disturbances; therefore, more insight into this subject is profitable. This study was conducted to investigate the spontaneous speech of older patients with LGGs in eloquent areas. METHOD: Thirty-four patients (22 males, 12 females) were included, and 21 healthy controls (8 males, 13 females) matched for age and education. Spontaneous speech from LGG patients was collected for analysis and served as an interview setting before awake craniotomy. The preliminary analysis shows that (i) only approximately 40% of the patients resumed a professional activity, (ii) the quality of life is altered, and (iii) despite the heterogeneity of the assessments, neuropsychological modifications seem mainly to concern attention and memory processes. CONCLUSION: As for the pediatric population, medulloblastoma adult survivors seem to present a late toxicity of the treatment. It justifies a discussion about the adaptation of the treatment modalities at least for the standard risk patients.

INTRODUCTION: Bortezomib-induced peripheral neuropathy (BIPN) presents in up to one-third of multiple myeloma (MM) patients treated with BTZ. The EORTC quality-of-life questionnaire, the QLQ-C30, has demonstrated to be reliable and valid when used with MM patients. The EORTC has developed the QLQ-CIPN20 questionnaire module to assess patients’ symptoms and functional limitations related to chemotherapy-induced peripheral neuropathy (PN). QLQ-CIPN20 consists of 20 items grouped into three scales assessing sensory, motor, and autonomic symptoms and functioning. The aim of the study was to determine the usefulness of the Spanish version of the QLQ-CIPN20 in a series of MM patients treated with BTZ. MATERIAL AND METHODS: A sample of 18 patients participating in a study evaluating the risk factors for developing BIPN (J. Peripher. Nerv Syst 2010;15:17–23) were asked to complete the QLQ-C30 and the QLQ-CIPN20 at baseline and during treatment. PN was graded according to the Total Neuropathy Score, both clinical (TNSc) and reduced (TNSr). QLQ-CIPN20 was compared to baseline between patients with and without PN, and at last visit between patients with and without BIPN. RESULTS: Prior to BTZ therapy, 6 patients had PN (5 had received vincristine previously). At baseline, patients with PN reported significantly more sensory (P < .01) and motor (P < .05) problems on the QLQ-CIPN20 than those without PN. Five of 18 patients developed BIPN. Patients with BIPN reported significantly more sensory problems than those without BIPN (P < .002) scale. No significant differences were observed on the final QLQ-CIPN20 in BIPN patients with or without prior PN at baseline. TNSc and TNSr baseline scores were significantly different between patients with and without PN (P < .001). Patients who developed BIPN showed differences in TNSc (P < .004) and TNSr (P < .048) when compared with patients without BIPN. In the whole series, TNS was significantly correlated with QLQ-CIPN20 sensory (TNSc: r = .52, P < .001; TNSr: r = .57, P < .01), motor (TNSc: r = .37, P = .001; TNSr: r = .36, P < .002) and autonomic (TNSc and TNSr: r = .59, P < .001) scales. CONCLUSION: Our results confirm the usefulness of this questionnaire in detecting the impact related with sensory impairment in BIPN patients. Besides, QLQ-CIPN20 scales exhibit a significant correlation with TNS.

INTRODUCTION: Fatigue and sometimes altered mood. A comparison with the preoperative condition was made. The agreement between the patient group and the controls in lexical diversity, repetition, self-corrections, and incomplete sentences. RESULTS: Statistical analyses revealed a significant difference (P < .01) between the patient group and the controls in lexical diversity, repetition, self-corrections, and incomplete sentences. In the patient group, repetitions occurred most frequently, followed by self-corrections, and incomplete sentences. Discussion: The results of this study suggest that a word finding deficit is the background of the disturbed spontaneous speech of LGG patients. The availability of different words is restricted.
P.026. CARING FOR A PATIENT WITH A MALIGNANT GLIOMA: AN ANALYSIS OF CARE-GIVER BURDEN
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BACKGROUND: The progressive and physical cognitive impairment experienced by patients with a malignant glioma (MG) places particular importance on the role of a patient’s primary caregiver. Providing care for a patient with MG can be particularly burdensome, impacting social, physical, and emotional quality of life (QOL). Given the importance of the caregiver in the course of treatment, the purpose of this study was to quantify and describe the impact and outcome of the caregiver’s experience. METHODS: Patients with MG within 6 months of initial diagnosis or relapse were eligible for this study if they had an involved caregiver. The Caregiver Quality of Life Index-Cancer (CQOLC) was given to caregivers at baseline as part of a series of validated instruments to assess involvement and impact on them. The CQOLC measures social, physical, and emotional strain on a caregiver through 35 items on 5-point Likert scales (0 = not at all to 4 = very much). The CQOLC has a maximum score of 140 points, with a higher score reflecting better QOL. RESULTS: Completed CQOLC questionnaires were collected from 22 caregivers to date. Of the 35 items, the 3 most strongly reported were increased levels of stress, distress over seeing their loved one deteriorate, and an increased fear of their loved one dying. The caregivers surveyed in this study scored an average of 80.6 on the 140-point scale. This is significantly lower (P = .01) than the average for caregivers across all cancers (93.3). We also found a significant difference between caregivers of patients with newly diagnosed vs recurrent MG. Caregivers of newly diagnosed patients were significantly more likely to feel sadness (P = .055) and feel that their life is imposed upon (P = .002), while caregivers of patients with recurrent MG were significantly more satisfied with their sex lives (P = .03).

CONCLUSIONS: Results demonstrate the heavy burden placed on caregivers of patients with MG, particularly for those caring for newly diagnosed patients. This burden is greater than that by caregivers of patients with other cancers; this may be related to the neurologic compromise of patients with MG. Caregivers play a crucial role in assisting MG patients; these findings demonstrate the negative impact on caregivers and the importance of the physician awareness so psychosocial interventions might be instituted.

P.027. HOW DOES TUMOR RESECTION AFFECT COGNITION? HIGH-GRADE GLIOMA VS MENINGIOMA PATIENTS
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INTRODUCTION: Many patients with intracranial tumors suffer from cognitive deficits. Because of differences in localization and growth speed, high-grade glioma (HGG) more readily damages healthy brain tissue compared with meningioma (MG). Surgical resection may diminish the pressure on adjacent tissue, but it may otherwise harm neuronal tissue. Our aim was to compare the effects of tumor resection on cognition in patients with HGG and with MG.

METHODS: Seventy-five patients (41 HGG, 34 MG) were tested preceding surgery. Testing was repeated following surgery. Reasons for drop-out included refusal, post-surgical stroke, and progressive tumor growth. For HGG patients, mean postoperative test scores—apart from perception—improved compared with presurgical levels. The improvement was significant for construction and speed. Changes in performance after surgery were not related to the extent of resection. For MG patients, mean preoperative test scores declined for perception (significantly), WM, and speed, while the other domains showed a nonsignificant increment compared with presurgery. All MG patients underwent a radical resection.

RESULTS: HGG patients have more cognitive deficits than MG patients. Surgery leads to an improvement of cognitive functioning in HGG patients, while this effect is less clear in MG patients. This might be because of a shorter test interval in HGG, or because more severe cognitive deficits in HGG patients may more easily improve than the subtle deficits associated with MG.

P.028. A NEW ORIENTAL MEDICAL APPROACH TO ELIMINATE BRAIN EDEMA COMPROMISED WITH MALIGNANT BRAIN TUMORS: EFFICACY OF GOREISAN (AN AQUAPORIN INHIBITOR)
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OBJECTIVES: Glyceral, steroids, and isosorbide, which are covered by Japanese national health insurance system, are widely used as medical decompression agents to eliminate brain edema complicated with malignant brain tumors and to relieve headache and several focal neurological deficits. Their side effects, however, sometimes prevent them from long-term use. For reducing brain edema, the authors have used the traditional oriental medical prescriptions for promoting diuresis and eliminating dampness, such as goreisan. Goreisan constitutes of 5 types of herbs-Polyergus 3 g, Rhizoma Alismatis 13 g, Rhiza Acanthopanacis 13 g, Radix Bupleuri 9 g, and Radix Orchidis 3 g. It is well known as an aquaporin inhibitor to suppress pathologically emerged aquaporin 4 which increases in various pathological conditions such as malignant brain tumor, trauma, cerebrovascular disease, and so on.

METHODS: Between October 2006 and February 2010, goreisan was prescribed to 63 cases (52 patients; males 29, females 23, ages range between 24 and 83 years, mean 55.4) with malignant brain tumors (primary tumor 16 patients and metastatic tumor 36 patients). Headaches were complained in 23 cases, and focal neurological deficits were complained in 44 cases. The efficacy was evaluated with improvement rate of symptoms and neurological deficits; excellent (improvement rate >50% and higher), good (improvement rate <50% and can significantly reduce the dose of glyceral and steroids), no effect, and deterioration. RESULTS: Excellent 18 (28.5%), good 30 (47.6%). No occurrence of the adverse reactions was recognized.

CONCLUSION: Goreisan can be used as a substitute for glycerol, isosorbide, and steroids to reduce mild brain edema.

P.029. STRENGTH OF SKELETAL MUSCLE IN Gliobloma Patients: An ongoing pilot study
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Glioblastoma (GBM) leads to a decrease in muscular strength as a result of neuromuscular dysfunction caused by GBM itself, and of corticosteroid treatment which is needed to decrease intracranial pressure. Aim of this pilot observation was to test feasibility of strength testing in GBM patients.

METHODS: Strength testing was so far performed in 2 patients (m = 4.1 years, 54 ± 16a, BMI = 28 ± 4 kg/m²) at baseline and follow-up after 5 (± 2) months. One patient (Patient 5) dropped out because of death before follow-up; Patient 4 started with a training program after receiving the GBM diagnosis, the other patients reported no muscular training activity. Handgrip strength was measured by using a Jamar hand dynamometer. Isokinetic testing of both thighs (isokinetic knee extension and flexion strength) was performed by using a Biodex 3 dynamometer.

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RESULTS: None of the patients showed side effects during or after the strength examinations. Handgrip strength of right hand/left hand measured for Patients 1–3: 16–62/10–44 (range) lb. Handgrip strength of dominant right hand increased in Patients 1, 2, and 4 (+9% to +10%), and decreased in patient 3 (−37%). Handgrip strength of left hand decreased in Patients 1–3 (−20% to −70%) (range), and increased in Patient 4 (+17%). Peak torques/weight (PT) of right knee extensors were in Patients 1–3: 91–290 (range) Nm/kg; PT of left knee extensors were 128–311 (range) Nm/kg. PT of right knee flexors were in Patients 1–5: 32–182 Nm/kg; PT of left knee flexors were 28–187 Nm/kg. At follow-up, isokinetic strength of knee extension and knee flexion decreased in 3 patients: extension of right knee from 32% to 18% (range) and flexion of right knee decreased by 3%. Extension of left knee decreased in all 4 patients (Patient 1: 4–5% to −51%). Flexion strength of both knees decreased in 3 patients (right knee: Patient 1–3: −16% to −59%; left knee: −22% to −32%). In Patient 4, isokinetic strength increased (+21%). CONCLUSION: Testing of muscular strength seems relevant in GBM patients. The results of this pilot observation indicate that strength of thigh muscles appears more than handgrip to decrease during the survival time. However, Patient 4 was able to increase his muscular strength through training.

P.031. THE NEURO-ONCOLOGY SPECIALIST NURSE: COORDINATING THE CARE OF PATIENTS WITH INTRACRANIAL TUMOR
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INTRODUCTION: In 2006, the National Institute for Clinical Excellence (NICE) published guidelines in the UK for the management of adult patients who are affected by brain tumors. The guidance advises that all patients diagnosed with an intracranial tumor should be allocated a “Key Worker” to coordinate their care. In most neuro-oncology units in the UK, this role is undertaken by the neuro-oncology specialist nurse (NOSN) and the majority of nurses are single-handed practitioners. OBJECTIVE: To identify the involvement of the NOSN in the management of patients with brain tumors. METHODS: Retrospective casenote review of NOSN involvement in the management of newly diagnosed patients with high grade glial tumors (HGGT), low grade glial tumors (LGGT), meningiomas and pituitary tumors. Data were collected from a single neurosurgeon in the period July 1, 2008–June 30, 2009. RESULTS: The records of 140 adult patients were reviewed (59 M: 81 F). The most common tumor types were HGGT (37%) and meningioma (31%). The frequency of NOSN involvement in patient management was: HGGT ≥75%; LGGT ≥69%; meningioma ≥51%; pituitary tumor ≥48%. Patient and carer contact with the NOSN was greatest in the HGGT group (frequent) with an average of 13 contacts. As a consequence, these contacts the NOSN liaised with 10 other health professionals on average. Patient and carer contact was lowest in the meningioma and pituitary tumor group.

CONCLUSION: NICE guidance recommends that all adult patients with brain tumors should have NOSN involvement in their care. This study suggests that we are nearing compliance in patients with compliance HGGT but there is still unmet need in patients in other tumor groups. There is a need to increase the number of NOSNs.

P.032. COGNITIVE REHABILITATION IN NEURO-ONCOLOGICAL PATIENTS
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INTRODUCTION: Still now, despite therapeutic achievements of last decades in oncology, neuro-oncological patients are characterized by poor prognosis and low quality of life (QoL) during disease progression. Among neurological deficits, cognitive decline is one of the most common symptoms, with a severe impact on patients’ QoL. As pharmacologic interventions have not proven effective yet in the treatment of cognitive deficits, cognitive rehabilitation could represent an alternative approach. Literature research (Medline) evidenced 5 studies about this topic. Although all studies reported some successes, these are difficult to interpret because of limitations in the methods used. Additionally, both type and time of interventions, study population, and outcome measures were different, making studies not comparable. MATERIALS AND METHODS: Fifty-five patients (mean age 51 ± 14.4 years, range 25–79 years) affected by primary brain tumors referred to Palliative Home-Care Unit for Brain Tumor Patients, Regina Elena National Cancer Institute (Rome), from June to December 2009 were evaluated. All patients had already undergone surgery and chemotherapy and/or radiotherapy. All patients underwent a comprehensive neuropsychological examination assessing memory, language, attention, executive functions, and visuo-constructional skills. On the basis of literature review, we identified basic criteria for assessment of patients requiring cognitive rehabilitation program: (i) mild-to-moderate cognitive deficits (MMSE ≥18); (ii) life expectancy >6 months; (iii) KPS ≥70; (iv) age ≥18 years. Also we defined a standardized program consisting in: 1-hour-weekly individual sessions, lasting 10 weeks, carried out with a computer program. At now we enrolled 8 patients who are performing rehabilitation training. CONCLUSIONS: Limited data about cognitive rehabilitation in neuro-oncological patients has left many questions about the suitability of interventions in this population unanswered. Optimal timing, type, and intensity of interventions are unknown. Similarly, the role of factors such as tumor grade, prognosis, fatigue, disease duration, severity of cognitive impairment must still be clarified to establish eligibility criteria for cognitive intervention.

IMMUNOLOGY AND IMMUNOTHERAPY

P.033+. INTENSE HUMAN CYTOMEGALOVIRUS (HCMV) IMMUNE RESPONSE IN GlioBLASTOMA PATIENTS: A NOVEL PROGNOSTIC FACTOR FOR SURVIVAL
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BACKGROUND: Glioblastoma is a lethal malignant brain tumor with overall survival rates of < 9.8% at 5 years. HCMV is a ubiquitous human herpesvirus found in nearly all humans worldwide with a persistent infection occurring in over 70% of adults. HCMV has been implicated in the development of several human malignancies owing to oncomodulatory effects of HCMV infection. It has been recently recognized that there exists an association between HCMV and malignant gliomas. Expression of HCMV nucleic acids and proteins has been described in >90% of gliomas in vivo. To study the prognostic value of anti-HCMV immune response in glioblastoma we prospectively assessed the levels of serum HCMV IgM and IgG in newly diagnosed glioblastoma patients and correlated the results with the clinical course. MATERIALS AND METHODS: Serum from 24 glioblastoma patients treated with standard chemo-radiotherapy in our institution between November 2008 and October 2009 were analyzed. Any HCMV IgM over 0.5 U/mL was considered diagnostic for acute HCMV infection. HCMV IgG >16 U/mL was regarded as positive for latent infection. Intense HCMV IgG immune response was defined as HCMV IgG >100 U/mL. All clinical and pathological data were recorded in a database
system using SPSS 13.0 statistics package. Response and progression-free survival time were defined, respectively, as objective response according to the 2D Macdonald criteria. Survival curves were generated using the Kaplan–Meier method and univariate analyses for survival differences were tested using two-sided log-rank tests. Cox’s proportional hazards regression model was used for multivariate analysis. RESULTS: After a median follow-up of 11.4 months, 13 patients (54%) have died. HCMV IgG was positive for latent infection in 9 patients (37%), 5 of whom had intense HCMV IgG immune response (20%). None of the patients had an acute HCMV infection. In univariate analysis, HCMV IgG >100U/mL demonstrated a strong significant association with a longer overall survival (P = .020). Positive HCMV IgG was found to be marginally associated with survival (P = .07). In multivariate analysis, the only prognostic factors that retained statistical significance were complete tumor resection and age ≥65 years. CONCLUSIONS: Intense HCMV IgG immune response is significantly associated with longer overall survival in our series. Further larger studies are required to validate HCMV IgG as prognostic factor for survival in glioblastoma patients.

P.034*. MODULATING THE IL-1 SIGNALING DURING GLIOMA ONCOLYTIC VIROThERAPY
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There are no effective treatments for glioblastoma (GBM), and patients with this cancer have a life expectancy of 15 months from diagnosis. This poor prognosis is because of the difficulty in delivering appropriately targeted drugs to the brain and infiltrating margins of GBM. Thus, the capacity of oncolytic viruses (OVs) to generate progeny on-site that can spread throughout the tumor represents an ideal strategy for GBM treatment. However, the host innate immune response reduces OV replication in vivo and limits their therapeutic potential. It is therefore crucial to understand the mechanisms regulating antiviral immunity to improve the OV efficacy. We have previously shown that intratumoral injection of OVs induces infiltration of phagocytes (macrophages and microglia) that inhibit viral replication and persistence. Pretreatment of animals with cyclophosphamide (CPA) depletes macrophages from the cancer stroma and OV spread and animal survival. However, the efficacy of the CPA + OV combined treatment is still poor. Indeed, more recent data indicated that macrophages are rapidly restored after CPA activity, leading to viral clearance, tumor re-growth, and animal death. Continuous systemic administration of CPA is toxic to the animals; therefore, it is important to find alternative means to prolong the immunosuppressive action of CPA in a more selective and less toxic fashion. We hypothesized that combination of CPA + OV armed with inhibitors of inflammation will prolong the immunosuppressive effects of CPA selectively in tumor tissue, thus resulting in enhancement of OV treatment while minimizing systemic toxicity. To test this hypothesis we have first identified the molecules that trigger OV-induced inflammation by analyzing tumor gene expression changes early after OV delivery. Our data showed 12 genes changing in expression; they were all induced by CPA and belonged to the interleukin (IL)-1b signaling. Interestingly, IL-1b is an inflammatory cytokine with strong tumorigenic properties and the antagonist for IL-1 receptor (IL-1RA) is being tested for cancer treatment. We have then observed that IL-1b is induced in glioma cells by a combination of serosal factors and OV infection and inhibits viral replication in vitro. Systemic pretreatment of animals with IL-1RA prevents OV-induced intratumoral macrophage infiltration and increases OV spread. IL-1RA is a protein and does not cross the blood–brain barrier; thus, when delivered systemically, it did not inhibit activation of macroglia in response to intratumoral OV. We expect that CPA + OV armed with IL-1RA will result in a broad suppression of phagocytic cells and synergistic enhancement of oncolytic virotherapy. Altogether, we have identified the intratumoral signaling initiating OV-induced inflammation and these data can be used in a new strategy of virotherapy for GBM that presents strong potential for a synergistic treatment outcome.

P.035*. T-CELL BASED IDENTIFICATION OF TISSUE ANTIGENS BY AUTOMATED TWO-DIMENSIONAL PROTEIN FRACTIONATION
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BACKGROUND: Here, we describe a new method to comprehensively identify candidate tissue antigens that spontaneously cause T-cell responses in disease situations. MATERIALS AND METHODS: We used the newly automated two-dimensional chromatography system P2FD to fractionate the proteome of tumor tissues and tested protein fractions for recognition by pre-existing tumor-specific CD4+ T-helper cells and cytotoxic T-cells. RESULTS: Applying this method to the ovalbumin (OVA) specific, TCRtg OT-I mouse model demonstrates efficient separation, processing, and cross-presentation to CD8+ T-cells by dendritic cells of OVA expressed by the OVA-transfected mouse lymphoma RAM-OVA. Applying this method to human tumor tissues, we identified in patients with head and neck cancer MUC-1 and EGFR as tumor-associated antigens selectively recognized by patients’ T-cells. Finally, we detected on an exemplary patient with a malignant brain tumor CD4+ and CD8+ T-cell responses against 2 novel antigens, trans-ferrin receptor and calgranulin B/S100A9, which were expressed on tumor and endothelial cells. Immunogenicity of these antigens could be confirmed in 4 out of 10 other brain tumor patients. CONCLUSIONS: This fast and cheap method appears suitable to identify candidate T-cell antigens in various disease situations, such as malignancies without restriction to their expression by a certain cell type or HLA allele.

P.036. HUMAN GLIOBLASTOMA CELLS DERIVED FROM NEUROPHERSES ARE MORE SENSITIVE TO NK, LECTIN-DEPENDENT, ANTIBODY-DEPENDENT, IL-2-ACTIVATED NK CELL LYSIS AND ANTI-TUMOR T-CELL CYTOTOXICITY COMPARED WITH CELLS FROM ADHERENT CULTURES DERIVED FROM IDENTICAL GBM PATIENTS
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Glioblastoma multiforme (GBM) is a brain tumor with a very poor prognosis as a result of inevitable recurrence. During the past few years, a contingent of cells within tumors, so-called stem-like tumor cells (STC), has been characterized in GBM. These cells have similar properties to neural stem cells and can, with a limited number of cells injected in vivo in animals, reconstitute entire tumors. They are also resistant to current radio- and chemo-therapeutic treatments in vitro. Therefore, STC are considered to play a key role in GBM recurrence observed in patients. These cells may be appealing targets for new therapeutic approaches such as immunotherapy. In this study, cells obtained from GBM specimen were grown in DMEM 10% FCS (adherent culture) and in serum-free medium supplemented with EGF and basic FGF (neuropherses culture). Phenotypic analyses confirm expression of stem cell markers such as CD133, nestin, and A2B5 on cells from neuropherses but not on cells from adherent cultures using cell lines derived from 5 different GBM patients. Expression of HLA class I molecules is observed in cells from both neuropherses and adherent cultures. Regards tumor antigen expression, IL13Ra2 antigen is only observed on adherent cells. In contrast, EGFRVIII is expressed at a higher level on cells from neuropherses compared with adherent cultures. Cell lines are then tested for their sensitivity to cell cytotoxicity mediated by NK and anti-tumor T cells. Human GBM cells grown as neuropherses are more sensitive to NK and CTL lysis compared with the same cells grown as adherent layers. Indeed, in contrast to their corresponding cells derived from adherent cultures, cells from neuropherses are sensitive to cell cytotoxicity mediated by resting NK cells or activated NK cells (with lectins, antibodies, and IL-2). In addition, Melan-A-pulsed cells from neuropherses pulsed are sensitive to Melan-A–specific T cell lines, used as effectors, compared with cells derived from adherent cultures. In total, this study demonstrates that STC are suitable targets for immunotherapy using NK or specific T cells as effectors.

P.037. STUDIES OF NATURAL KILLER (NK) CELLS AGAINST GLIOMA INITIATING CELLS IN VITRO
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BACKGROUND AND OBJECTIVE: There is increasing evidence sustained the hypothesis that human gliomas originated from glioma-initiating cells or stem cells (GIC/GSC). And usually these cells could not be eradicated by conventional surgery, chemotherapy, and radiotherapy because of their stem-like properties. The cytotoxicity of activated natural killer (NK) cells against GIC in vitro was investigated. METHODS: The CD133+ glioma
cells were isolated from resected human glioblastoma specimens or glioma cell line and were used as GIC. The NK cells were separated from peripheral blood mononuclear cells of glioma patients or healthy donors by Miltenyi magnetic beads, and were activated with IL2/PHA. Their in vitro cytotoxicity against GIC was assessed by lactate dehydrogenase (LDH) assay, with K562 cells as positive control target cells. RESULTS: The allogeneic NK cells could be cultured and activated with GIC-cultured medium, the increased cytolytic activity against GIC was shown with the higher E/T ratio. At the same E/T ratio, the activated NK cells showed remarkable higher cytolytic activity against GIC than that of resting (freshly isolated) NK cells (P < 0.01). CONCLUSIONS: The allogeneic NK cells could be activated in the GIC culture system and showed killing effect against GIC. It was suggested that activated NK cells might be used in the clinic for GIC eradication.

IN VITRO/IN VIVO MODELS

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

P.039*. HIGH-RESOLUTION NMR SPECTROCOPY OF BRAIN-DERIVED STEM CELLS
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NMR spectroscopy of living organisms provides a noninvasive and comprehensive insight into cellular composition and metabolism. In addition, identifying cell-specific NMR spectroscopic signals and patterns may lead to in vivo detection and tracking of different cell types including stem cells. We established high-resolution 1H-NMR spectroscopy of several cultured brain-derived stem/progenitor cell lines like Nestin-positive fetal murine neural progenitors (NPCs), DCX-positive adult murine neuroblasts, and CD133+ human glioblastoma-derived cancer stem cells (CSCs), all cultured under serum-free conditions. Measurements are performed at Bruker Avance 600 MHz (14.4 T) and 800 MHz (18.8 T) spectrometers equipped with TCI cryo probes. Employing a metabolomic approach including spectroscopic filtering techniques, sophisticated quantification methods, and correlation analysis of spectroscopic and biological data, we investigate both metabolites and NMR-visible macromolecules (ie, so-called mobile lipids and macromolecules) on the one hand, and on the other hand the possibility of monitoring neurogenesis, neurodegenerative diseases, and tumors regarding both diagnosis and therapy noninvasively in vivo in humans.

PREDICTIVE BIOMOLECULAR MARKERS

P.040*. SCREENING CHEMOTHERAPY AGENTS USING SURGICALLY OBTAINED BRAIN TUMOR SPECIMENS
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BACKGROUND: Surgical brain tumor specimens can be obtained valuable information regarding sensitivity to drug therapies. Data collected on surgical specimens using an in vitro growth and invasion assay were correlated with patient response to chemotherapy. METHODS: Surgically obtained glioma tumor specimens were cultured in a 3-dimensional collagen gel matrix and observed for growth and invasion. Chemotherapy drug effects on mean invasion and growth were expressed as a ratio relative to control conditions. Temozolomide (TMZ) sensitivity was correlated with methyl-guanine-methyl transferase (MGMT) methylation status. Length of patient survival was compared between TMZ-treated patients whose screening results had predicted a positive response and those predicted to have a negative response. RESULTS: Tumors from individual patients differed in terms of response profiles, especially when response was defined as at least an 80% reduction in tumor invasion distance. Similarly, different drugs varied in their ability to inhibit tumor growth and invasion, with only 31% (29%) tumors responding to TMZ, compared with 100%, 94%, and 90% response rates for paclitaxel, cis-platinum, and vincristine, respectively. Length of survival in TMZ-treated patients who screened positive for a TMZ response averaged 301 days, vs just 98 days in their TMZ-negative counterparts. CONCLUSIONS: In this study, we report a novel assay system that generates individual patient drug profiles, and an ability to predict patient survival in TMZ-treated patients. Further research, including a formal prospective clinical trial, may be warranted.
INTRODUCTION: Erythropoietin (Epo) is a well-known factor of erythropoiesis and is therefore used to treat anemia in neoplastic disease. In addition, Epo exerts neuroprotective effects via Epo-receptor (EpoR) on neuronal cells. This makes a prophylactic use against neurocognitive impairment caused by radiochemotherapy probable. Epo-EpoR signaling, however, has also been recognized in various tumors such as glioblastomas. Several studies during the last years performed in vitro and in vivo reported conflicting results on the effect of Epo on malignant gliomas. We analyzed here the impact of Epo and EpoR expression on the prognosis of human glioblastomas in different treatment groups. METHODS: We established a retrospective bank of human glioblastomas with complete documentation of clinical course and treatment. The expression of Epo (n = 64) and EpoR (n = 66) was assessed by immunohistochemistry and analyzed with semiquantitative scores. The results were assessed separately for short- or long-term survival in the treatment groups by univariate and multivariate analysis with respect to age, gender, chemotherapy, and extent of resection. RESULTS: High expression levels of EpoR were correlated with a median survival advantage of 8 months (P < .01) in patients under 60 years of age. High levels of both Epo and EpoR were associated with a significant prolongation of median survival when compared with low levels of both molecules. In patients treated with radiochemotherapy adjuvant to operation, a trend to 6-month longer median survival was observed in association with high levels of EpoR expression that just failed significance (P = .06). In the multivariate survival analysis, a positive correlation of EpoR with long patient survival proved to be significant. DISCUSSION: In accordance with some of the previous studies, we found evidence for a longer patient survival associated with higher expression levels of EpoR in human glioblastomas. A therapeutic use of Epo for anemia in glioblastoma patients seems therefore to be safe with respect to tumor growth. A prophylactic use (ie, for neuroprotection, however) cannot be recommended in light of the functional studies described in the literature.
P.046. IDH1 AND IDH2 MUTATIONS AND THEIR CORRELATIONS IN GLIOMAS
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INTRODUCTION: Somatic mutations of isocitrate dehydrogenase enzyme isoforms 1 (IDH1) and 2 (IDH2) have been recently described in a high percentage of diffuse gliomas and oligodendrogliomas. The two isoforms catalyze the conversion of isocitrate to α-ketoglutarate with reduction of NADP+. Mutations are preferentially located in exon 4 of both IDH1 and IDH2 genes, affecting arginine at codon 132 (R132) of IDH1 gene and the codon 172 (R172) of IDH2 gene. MATERIALS AND METHODS: Search for mutations in IDH1 and IDH2 genes was investigated in a series of 120 grade IV (glioblastomas), 32 grade III (10 astrocytomas and 22 oligodendroglias), and 44 grade II–I gliomas (10 pilocytic astrocytomas, 10 diffuse astrocytomas, 24 oligodendroglias). Analysis was performed on formalin-fixed and paraffin-embedded surgical samples by direct sequencing. RESULTS: Distribution of IDH1 mutations was inversely correlated with histological grade, occurring in 50% of diffuse astrocytomas grade II, 10% of pilocytic astrocytomas, 75% of oligodendroglias grade II, 36% of oligodendroglias grade III, and 2% of tumors grade IV. The majority of mutations were in IDH1 gene: R132H accounting for 91% of cases, R132Q for 6% and R132C for 3%. Those of IDH2 gene (R172K) were limited to 1 glioblastoma and to 1 oligodendroglioma. Associations of IDH1 mutations were tested for the following molecular markers: MGMT hypermethylation, LOH of 1p/19q, EGFR amplification, and TP53 mutations. IDH1 mutations showed a trend towards a positive association with MGMT hypermethylation and LOH of 1p/19q, whereas they were mutually exclusive with EGFR amplification (P = .0346). CONCLUSIONS: IDH1 and IDH2 mutations may represent an early genetic event in gliomagenesis, preceding the differentiation of precursors, and may be considered prognostic. It is conceivable that they are preserved in secondary glioblastomas. The latter must be rather rare in our collection where none of the glioblastomas was diagnosed at a second surgery after a previous astrocytoma.

P.047. SERUM S-100B PROTEIN IS A PREDICTOR OF SURVIVAL IN RECURRENT GLIOMA
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BACKGROUND: S-100B protein is raised in serum after cerebral damage and is used as a marker for the progression of the disease. It is not specific for glioma, but seems to be a useful marker for the evaluation of response to therapy. PATIENTS AND METHODS: Serial samples of 22 patients with recurrent glioma or GBM were obtained before, during, and after chemotherapy. Serum S-100B was measured and a Kaplan–Meier curve was drawn for high and low serum concentrations. RESULTS: Recurrent glioma patients with a high serum concentration of S-100B at baseline had a significantly shorter survival compared with patients with a low concentration (P = .000). No trends were detectable in serial measurements. No correlation was found between S-100B concentration and age, gender, tumor pathology, or response to chemotherapy. CONCLUSION: In patients with recurrent glioma, serum concentration S-100B is a strong predictor for survival.

P.048. TEMOZOLAMIDE AND RADIOTHERAPY IN NEWLY DIAGNOSED GLOBLASTOMA PATIENTS: MGMT PROMOTOR METHYLATION STATUS AND Ki-67 AS BIOMARKERS FOR SURVIVAL AND RESPONSE TO TREATMENT
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AIMs: This phase II study aims at investigating the correlation between O6-methylguanine DNA methyltransferase (MGMT) promoter methylation status and Ki-67 label index, and response to temozolomide (TTP) and overall survival (OS) in newly diagnosed patients with glioblastoma (GBM) who are treated with temozolomide (TMZ) concomitantly with and adjuvant to radiotherapy (RT). PATIENTS AND METHODS: From June 2005 to [Unsupported Character] August 2008, 34 patients with newly diagnosed GBM received TMZ 75 mg/m2 as radioisotizer plus RT 2 Gy/treatment up to 60 Gy, followed by TMZ 175 mg/m² for 5 days every 4 weeks for 12 doses. Methylation-specific PCR assay and Ki-67 expression were performed on the tissue blocks. The patients were followed by MRI while MR spectroscopy (MRS) was performed to confirm progression and accordingly bevacizumab 10 mg/kg every 2 weeks was added to 7 patients till further progression was proved. RESULTS: Three patients were lost to follow up and tissue specimens were not available for 5 patients. Mutations in MGMT (38.7%) had unmethylated MGMT, whereas 19 (61.3%) were methylated, the cut off value of Ki-67 in relation to survival was 17%, where 15 specimens were <17% (48.4%), and 16 were ≥17% (51.6%). The overall disease control rate (CR, PR, SD) was 42.4%, where 8 patients (23.5%) had a median OS of 12 months and the median OS was 20 months, the methylated patients had a higher median TTP of 13 months (range 8–18 months, CI 95% of 9.36–12.9), and OS of 24 months (range 12–31 months, CI 95% of 16.1–21.3), while the unmethylated patients had a median TTP of 6.5 months and a median OS of 12 months which was highly significant (P = .0001). Patients with Ki-67 <17% had a median TTP of 16 months and median of OS of 24 months compared with 7 and 12.5 months, respectively, for the patients with Ki-67 ≥17%. The multivariate analysis of both methylated MGMT status and Ki-67 showed a nonsignificant correlation to ODC, TTP, and OS. Significant correlation was found between the ODC, TTP, and OS with age <52 years (P = 0.001), tumor excision vs biopsy (P = 0.001), and the number of TMZ doses received ≥10 doses (P = 0.002). The commonest G3 and G4 toxicities were lymphopenia and neutropenia in 3 patients (9.67%), thrombocytopenia in 4 patients (12.9%), and 1 patient with G3 constipations (3%), all were medically manageable. CONCLUSION: This study showed that MGMT promoter methylation status and the Ki-67 status could serve as independent predictive and prognostic markers of survival and response, they also might identify a group of patients who could benefit from combining further therapeutic agents to the TMZ.

P.049. EVALUATION OF IMMUNOMARKER AND ABSOLUTE PLATELET COUNT CHANGES AS PREDICTORS OF SEVERE THROMBOCYTOPENIA IN MALIGNANT GLIOMA PATIENTS TREATED WITH TEMOZOLOMIDE
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BACKGROUND: Temozolomide (TMZ) is commonly used for therapy of malignant glioma and induces severe thrombocytopenia in a small fraction of patients. Currently, no biomarkers predicting TMZ-induced thrombocytopenia are available. In this study, we investigated whether changes in platelet count (PLT) or the immature platelet fraction (IPF) may serve as predictor of TMZ-induced thrombocytopenia in malignant glioma patients. The IPF has been suggested to reflect platelet turnover and may serve as an additional parameter for the differentiation and monitoring of several forms of thrombocytopenia including chemotherapy-induced myelosuppression. METHODS: We prospectively included 52 malignant glioma patients receiving TMZ-containing therapy regimens in this study. Platelet counts and IPF were determined at each clinical follow-up visit (weekly during concomitant to radiochemotherapy or at least monthly during adjuvant TMZ monotherapy) using the Sysmex XE-2100 system. RESULTS: The highest combination of sensitivity and specificity was observed for a PLT change of 0.5 x 10000/L at this cutpoint, the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for prediction of significant thrombocytopenia (<100,000/µL) were 80%, 50%, 66%, and 98%, respectively. The
highest combination of sensitivity and specificity was observed for an IFP change of 0.014 percentage-points per day. At this cutpoint, the sensitivity, specificity, PPV, and NPV for prediction of significant thrombocytopenia were 60%, 67%, 7%, and 97%, respectively. CONCLUSIONS: Low sensitiv- ity, specificity, and PPV indicate that the time course of PTL counts and IFP measured at routine clinical follow-up are not useful for prediction of thrombo- cytopenia in gloma patients treated with TMZ.

P.050. IDH1 MUTATION IS AN IMPORTANT FACTOR PREDICTING OUTCOME IN HIGH GRADE GLIOMAS

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

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

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Brain tumors, in particular gliomas, are characterized by high mortality rate. However, gliomas with similar features often show different behavior. This raises the issue about molecular markers for prognosis prediction. Recently, somatic mutations in IDH1, which encodes cytoplasmic isocitrate dehydrogenase I, were reported to occur at high frequency in glioblastoma and association with overall survival was found. Genetic aberrations in IDH1 were predominantly detected in tumors that harbor TP53 mutations and mutations at codon 248 and 273 were associated with good prognosis. To determine prognostic value of IDH1 and TP53 mutations in Bulgarian patients, 30 glial tumors of various grades were selected and DNA was extracted from them. All samples were examined by direct sequencing for IDH1 and exon 5–8 of TP53. Mutations in IDH1 were found in 8 (27%) glial tumor. All genetic aberrations were located at position 395 and caused amino acid substitution R132H. Patients with IDH1 mutations were younger (median age 35.5 vs 54 in non-mutated cases; P = .001) and had better overall survival (median survival 32.1 vs 5 months in non-mutated cases; P = .01). Mutations in TP53 were detected in 7 (23%) tumor samples. Patients with mutated TP53 showed increased in overall survival (median survival 38.9 vs 5.4 months in non-mutated cases; P = .007). Genetic alterations in TP53 were found in 4 (50%) tumors with mutated IDH1 and 3 (13.6%) gliomas without IDH1 mutation. Median survival of patients harboring mutations in both genes was 43.8 months, while median survival of those with mutation in one of the genes and nonmutated cases was 31.6 and 6 months, respectively. Our results indicate that together IDH1 and TP53 mutations identify gliomas with better survival and may be applied as prognostic biomarkers in Bulgarian patients with gliomas.

P.052. PROMOTOR HYPERMETHYLATION-MEDIATED DOWN-REGULATION OF RUNX3 GENE IN HUMAN BRAIN TUMORS

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Brain tumors are usually caused by a change in genetic structure. Methylation of promoter regions, with corresponding downregulation of gene expression, has been highlighted as an alternative mechanism for tumor suppressor gene inactivation. Runt-related (Runx) proteins are tissue- restricted and cancer-related transcription factors that regulate cell proliferation and differentiation. RUNX3, the smallest protein of the Runx family, has been shown to play an important role in neuronal development, localized at 13p6 and its loss leads to tumorigenesis. We aimed to evaluate the methylation-mediated expression regulation of RUNX3 gene in brain tumors.

Cases (10 females, 11 males) were recruited into the study that have been diagnosed as brain tumors (3 meningiomas, 3 anaplastic astrocytoma, 3 diffuse astrocytoma, 12 GBM) and taken the decision of surgical operation. The mean age was 52.43 ± 15.33. Explant cell cultures were performed. Total RNA was isolated. Real-time quantitative RT-PCR analyses of RUNX3 gene were actualized. Genomic DNA and the bisulphate modification were performed for DNA methylation analysis. Quantitative methylation-specific PCR was used and primer pairs were designed. There was no signifi- cant difference between methylated and unmethylated quantitative ratio of RUNX3 gene promoter region and gene expression relative ratio. Methylated and unmethylated ratio in anaplastic astrocytoma, diffuse astrocy- tona, GBM, meningioma, and in all groups were: 1.44, 1.09, 1.51, 1.52 vs 1.43, respectively. One allele was found methylated necessarily. No methylation was detected in GBM and anaplastic astrocytoma groups of each case. Ranx3 promoter was found unmethylated in both of the GBM cases. There were significant differences between relative ratio of RUNX3 gene expression and methylated/unmethylated ratio rate, compared with all groups (P = .001) and compared with GBM groups (P = .041). This study overemphasized the RUNX3 gene importance in brain tumors, as a result of the existence at least one methylated allele.

P.053. BEVACIZUMAB-BASED THERAPY RECURRENT MALIGNANT GLIOMA: CORRELATION BETWEEN SERUM VEGF AND RESPONSE TO TREATMENT

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BACKGROUND: Significant therapeutic benefit has been observed for recurrent malignant glioma (MG) patients treated with bevacizumab (BV), a neutralizing monoclonal antibody against the vascular endothelial growth factor (VEGF). However, VEGF levels and response to BV has never been addressed so far. METHODS: We conducted a prospective analysis of recurrent MG patients treated with BV alone or in combination with chemotherapy performing serial evaluations of serum and plasma VEGF (sVEGF) and VEGF levels and procoagulant factors such as Tissue Factor (TF) and Thrombin/Antithrombin Complex (TAT) plasma levels (ELISA). Baseline, and post-treatment samples were collected at each administration of BV. RESULTS: Eighteen recurrent MGs (glioblastoma = 7, anaplastic astrocytoma = 7, oligodendroglioma = 4) who received BV at 10 mg/kg intravenously every 14 days, of whom 13 in association with chemotherapy were included in the study. Median age was 39 years (27–65), and median
of therapeutics is the blood–brain barrier (BBB), which is largely intact in regions where invasive cells reside. Glutathione (GSH)-conjugated PEGylated liposomes may be suitable vehicles for targeted delivery of small molecule cytotoxic drugs across the BBB. GSH is a natural anti-oxidant that is found at high levels in the brain and its active transporter is abundantly expressed at the BBB. Previous studies using microdialysis with an increasing % of GSH conjugated to liposomes carrying ribavirin have shown a % GSH-dependent increase of drug levels in brain interstitial fluid (up to 5-fold higher), and GSH-liposomes carrying endomorpin-1 were more effective in hot-plate tests when compared with unconjugated liposomes. We have now tested GSH-conjugated PEGylated liposomes containing doxorubicin (GSH-Doxil) for treatment of mice carrying intracranial U87 xenografts. In a first series, we compared 5% GSH-Doxil to conventional Doxil, free doxorubicin (Dx), and untreated controls. Mice were injected with 10 × 3 U87-luc cells and bioluminescence (BL) imaging was used for follow-up. After 11 days, mice were stratified into control or test groups (n = 9 / group). Mice received 3 consecutive weekly dosing of 5 mg/kg Doxil-equivalents. The cohorts receiving Doxil and Dx showed a marginal growth delay relative to controls. The response with 5% GSH-Doxil was more promising but variable: two animals receiving 5% GSH-Doxil showed complete regression, which was not observed in any of the other cohorts, whereas other tumors in this cohort responded more similar to the other treatment groups. Since the treatment was well tolerated, we performed another more dose-intensive series, administering biweekly 5 mg/kg Doxil-equivalents. Moreover, 5% GSH-Doxil and 5% GSH-Doxil were tested relative to Doxil and untreated controls. Treatment started at Day 14 after tumor cell injection, stratifying only animals whose tumor BL signals increased relative to Day 11. After Day 25, the animals experienced weight loss and precluded further testing. In this series, the variable tumor response was small. There was again one complete regression in the cohort of 5% GSH and not in any of the other cohorts. Moreover, the growth delay in the other tumors in this 5% GSH-Doxil cohort was significantly longer than in any of the other treatment groups. This growth delay resulted in a significantly increased median survival of 32.5 days relative to 27 days for untreated controls. The response in the 5% GSH and Doxil cohorts was marginally better relative to controls Overall, these results warrant further preclinical and clinical investigation using 5% GSH-Doxil liposomes.

NEUROIMAGING OF BRAIN TUMORS

P.056. ROUTINE FOLLOW-UP IMAGING AFTER TREATMENT FOR GLOBLASTOMA: HOW USEFUL IS IT? D. Nesbit, G. Hendry, D. Scoones, and P. Kane; Department of Neurosurgery, The James Cook University Hospital, Middlesbrough, UK

INTRODUCTION: Glioblastoma multiforme (GBM) is the most common and most malignant primary brain tumor (MPBT). It is common practice in Neuro-Oncology centers to use cranial imaging in the posttreatment follow-up of patients diagnosed with GBM. However, there is little published guidance regarding the recommended timing and frequency of follow up imaging and the efficacy of imaging in detecting asymptomatic tumor recurrence. OBJECTIVES: Our local Neuro-Oncology guidance recommends that patients diagnosed with GBM are CT scanned at 3 months (defined as 12 ± 2 weeks) post treatment and thereafter at 3 monthly intervals. This audit assessed compliance with local guidelines and performance in detecting asymptomatic recurrence. METHODS: Retrospective review of case notes. Data collected regarding post-treatment imaging modality, frequency, indication, and detection of symptomatic/asymptomatic tumor recurrence. RESULTS: One hundred sixty-two patients diagnosed with GBM were identified between 2004 and 2008. One hundred fifty-six cases were analyzed. 55 (35%) patients did not receive any follow-up imaging, explained in part by high patient mortality (median survival 35 weeks from time of diagnosis) and the proportion of patients receiving palliative care where follow up imaging was not indicated. Two hundred sixty-five scans were performed on 100 patients, 54% of which were within the 12 ± 2 week target. Thirty-two percent of scans were performed earlier than the 12 ± 2 week target. 36% were undertaken because of a clinical deterioration in the patient, the main reason for the reduced time interval between scans. Of 124 recurrences detected, 11 were asymptomatic. CONCLUSIONS: Guidelines relating to the follow up imaging of MPBT are limited. The National Institute for Clinical Excellence (UK) and the European Society for Medical Oncology recommend the use of cranial imaging in MPBT follow up, stating 3–4 monthly scans is ‘common practice’. Neither specifies the optimal timing or frequency of post treatment scans. The National Comprehensive Cancer Network (USA) recommends post treatment scans every 2–3 months post MPBT treatment, as does the Cancer Council Australia. There is lack of consensus and evidence regarding the post treatment imaging in patients with MPBT. Further studies are required to evaluate clinical and cost effectiveness.

NEW DRUG DELIVERY METHODS

P.055∗. GSHPOLYMER IMPROVES EFFICACY OF DOXIL AGAINST INTRACRANIAL XENOGRAFTS O. van Tellingen1, D. Brandsma1, W. Booger1, C. Appeldoorn1, F. Manca2, J. Rip2, R. Dorland1, J. van Kregen3, and P. Gaillard1; 1Hollands Cancer Institute, Amsterdam, Netherlands; 2BBB Technologies B.V., Leiden, Netherlands

High-grade glioma is a uniformly fatal disease with an unmet need for better therapy. A major reason for this poor outcome is the invasive nature of gliomas. Novel therapies that target invasive brain tumor cells should be invented, but a major impediment to the delivery of functional proteins is that their expression by immune system cells should be validated to avoid the progressive nature of tumors and target cells with molecular abnormalities.
P.057*. PERI-ICTAL PSEUDO-PROGRESSION IN BRAIN TUMOR PATIENTS
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BACKGROUND: During the follow-up of brain tumor patients, the appearance of new contrast-enhancing lesions on MRI frequently occurs in the context of disease progression. However, conditions such as early or delayed radiation necrosis can mimic tumor progression and are important to recognize to avoid futile therapeutic escalation. Transient peri-ictal MRI changes have been described in epileptic patients and some reports have suggested that changes can also mimic disease progression in brain tumor’s patients. However, the clinical and MRI features of these patients have not been specifically studied yet. METHODS: The databases of four institutions were consulted to identify brain tumor patients who presented during the follow-up period transient MRI lesions wrongly suggesting tumor progression in a context of epileptic seizures. RESULTS: Seven patients were identified. Five patients suffered from high-grade gliomas, one from a medulloblastoma and one from a single brain metastasis. All patients had been initially treated with surgery and radiotherapy and all had achieved a complete remission. The peri-ictal pseudo-progression episode occurred after a mean delay of 13.3 ± 8.6 years after radiotherapy (range 3–25). All patients demonstrated new focal neurological signs in a context of frequent epileptic seizures. The MRI features were highly similar across patients and consisted of focal cortical and/or leptomeningeal enhancing lesions that could extend beyond the initial tumor localization. The clinical situation progressively improved after adjustment of antiepileptic drugs and transient oral corticotherapy. MRI was normalized at 3 months in 4 patients and at 6 months in the others. Three patients demonstrated two or more relapses with the same clino-radiological pattern. At last follow-up, after a mean period of 3.7 ± 2.5 years (range 1–7) since the initial peri-ictal pseudo-progression episode, two of the patients had presented a tumor recurrence.

CONCLUSIONS: In brain tumor patients, especially in long-term survivors treated with radiotherapy, the appearance of new cortical and/or leptomeningeal contrast enhancing lesions in a context of seizures should raise the suspicion of pseudo-progression. We make the hypothesis that this phenomenon is in relation with a post-irradiation cortical vasculopathy.

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

MATERIALS AND METHODS: MRI scans, corresponding audiograms (with results of pure tone audiogram (PTA) and speech discrimination score (SDS)) of 63 patients, were analyzed retrospectively. Of 56 patients, 2 or more MRI/audiogram combinations were available. Mean follow up was 21.6 months. Volume measurements were performed on contrast enhanced T1-weighted images (CE T1-WI). Morphology was evaluated by checking the presence of central nonenhancement, VS stage and side and signal intensity of the affected labyrinth. Clinical charts were analyzed for symptoms. RESULTS: Growth occurred irrespective of hearing status (PTA/SDS), patient age, gender, VS side, symptoms at presentation and morphology (VS stage, nonenhancement, labyrinthine signal intensity), although significant growth in the first year was predicting further growth during FU. Patients complaining of sensorineural hearing loss (SNHL) showed significant worse hearing on PTA and SDS and a trend towards more profound hearing deterioration over time was seen. Hypointensity of the affected labyrinth was a predictive factor of significant hearing loss over time compared with isointense labyrinths. Volume measurements did not correlate with audiological function and deterioration. CONCLUSION: Hearing loss was more profound, and hearing will deteriorate faster in patients presenting with SNHL. Hypointensity of the affected labyrinth will result in a significant faster detoriation of PTA. Audiological deterioration occurs irrespective of VS growth and significant growth during the first year of FU predicts further growth during FU. No other factors predicting growth were identified, therefore sequential MRI remains the only objective FU method of conservatively followed vs Volume measurements are not a reliable measure predicting auditory function, in a W&ScS policy. These findings can aid the clinician dealing with VS patients in a W&ScS policy.

P.059*. MRI AND THALLIUM-201 SPECT IN THE PREDICTION OF OUTCOME IN GLIOMA THERAPY
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BACKGROUND: The prediction of outcome and the detection of tumor progression in glioma patients are of great clinical importance. In previous studies, we found 201Tl SPECT to be superior to conventional CT and MRI in the prediction of outcome during chemotherapy for recurrent glioma. The present study aims to study the value of MRI and 201Tl SPECT in the prediction of outcome in glioma patients treated with temozolomide and to optimize tumor follow-up by means of combined imaging (MRI and 201Tl SPECT).

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

P.060*. ANALYZING RESPONSE OF MALIGNANT GLIOMA TO BEVACIZUMAB USING HIGH-RESOLUTION MAGNETIC RESONANCE IMAGING AT 7 TESLA
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BACKGROUND: Glioblastoma is a highly angiogenic tumor. Therapy with the monoclonal anti-vascular endothelial growth factor (VEGF) antibody bevacizumab aims at inhibiting neo-angiogenesis and has shown promising results in phase II trials in recurrent glioblastoma. However, the effect of bevacizumab has not been adequately investigated in vivo so far. In this study, we analyze the effect of bevacizumab therapy on recurrent glioblastoma and the vasculature using high-resolution magnetic resonance imaging (MRI) at 7 Tesla including susceptibility-weighted imaging (SWI).

METHODS: We performed repeated 7-Tesla MRI investigations in 4 male and 2 female patients with recurrent glioblastoma receiving bevacizumab therapy. MRI investigations were performed at baseline and 2, 4, and 8 weeks after start of treatment. Each MRI measurement was performed within 48 hours before bevacizumab administration. A three-dimensional, fully first-order flow-compensated gradient-echo sequence with a TE of 15 ms was performed to acquire SWI data. T1-weighted data were acquired using an MP-RAGE sequence with the following parameters: image-matrix = 320 × 320; resolution = 0.75 × 0.75 × 0.7 mm; slices = 208; parallel imaging factor = 2, TR/TE/TI = 380/1700/3.55 ms, acquisition time = 10:29 minutes. Contrast agent was injected intravenously before T1-weighted measurement. RESULTS: Image quality was in general excellent, although in few investigations image quality was impaired by movement artifacts caused by neurological symptoms. In 3 of 6 patients we found marked and rapid decrease of brain edema after initiation of bevacizumab therapy. In 2 patients we observed an increase of SWI signals already at the first follow-up MR investigation 2 weeks after initiation of bevacizumab therapy. Both patients developed progressive neurological worsening and bevacizumab therapy had to be suspended because of tumor progression after 6 and 8 weeks, respectively. In 1 patient showing rapid decrease of contrast enhancement and sustained clinical improvement under bevacizumab therapy.
therapy, SWI signals remained unchanged at all 7-Tesla MRI investigations. CONCLUSIONS: High-resolution 7-Tesla MRI is feasible in patients with malignant glioma. Our data indicate that in a fraction of recurrent glioblastoma patients early growth of tumor vasculature occurs despite bevacizumab therapy (“primary bevacizumab resistance”). Advanced imaging modalities may improve assessment of response to bevacizumab therapy.

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

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OBJECTIVES: To analyze whether Thallium-SPECT is a good method to evaluate response to bevacizumab in recurrent HGG patients. METHODS: Seventeen patients with recurrent HGG who were considered for treatment with bevacizumab were included in a study and were treated with SPECT and MRI, before and after treatment, in order to evaluate response correlation. PATIENT CHARACTERISTICS: Twelve out of 17 patients could be evaluated with both techniques: 1 in 16 patients presented a previous positive SPECT, 4 patients progressed before imaging evaluation. Male/female ratio was 9/3. There were 10 GBMs out of 12. Previous surgery was biopsy in 5 cases, and partial or complete resection in 7. Regarding previous treatment, Stupp regimen was administered in 6 cases. Number previous chemotherapy lines >2 were 7/12. KPS >60% was in 11/12 and Barthel I >60% in 11/12. Evaluated treatment was as follows: Bev 2/12 or Bev and Iri 10/12. RESULTS: Response rate by MRI was as follows: P 41.7%, SD 8.3%, PR 16.7%, CR 25%. Response rate by SPECT was as follows: P 16.7%, SD 41.7%, PR 8.3%, CR 8.3%. Coincidence between SPECT and MRI was 24.9% and SPECT with Macdonald’s criteria was 16.6%. The sole patient with a CR by MRI and Macdonald’s modified criteria had a normalization of a previous positive SPECT lasting for 103+ weeks while continuous maintenance Bev. CONCLUSIONS: In spite of reduced number of patients, it seems that Thallium SPECT is not a good imaging method to evaluate response of bevacizumab treatment.

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

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

P.063*, MAGNETIC RESONANCE IMAGING OF VIRAL SPREAD AND INTRATUMORAL INFLAMMATION DURING ONCOLYTIC VIROThERAPY

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One of the major drawbacks in treating gliomas is the poor efficiency of drug delivery. Oncolytic viruses (OVs) that can selectively replicate in tumor cells and potentially can reach the infiltrating margins of the tumor, represent a promising tool to overcome this problem. However, the in vivo therapeutic effect of OV is limited because of host factors. We have recently demonstrated that the capacity of OVs to spread in vivo through the tumor is inhibited by intratumoral infiltration of phagocytic microglia and peripheral macrophages. Combining OVs with immune suppressive drugs can therefore increase their spread and therapeutic efficacy. However, the lack of a noninvasive imaging technique to detect intratumoral OV spread and phagocytic infiltration constitutes an important limitation in evaluating the results of new therapeutic strategies. We have tested 2 noninvasive magnetic resonance imaging techniques. The first one uses a gadolinium-based contrast agent to detect myeloperoxidase (MPO) activity, an enzyme present in phagocytic cells. MRI images show increased MPO activity after OV delivery. This enzymatic activity is reduced when animals are pretreated with cyclophosphamide. The MRI data correlate with immunohistochemical staining of phagocytic cells and ex vivo measured MPO mRNA levels and activity. We also show that this technique presents a unique spatial resolution whereby the inflammation process at the border and in the center of the tumor can be distinguished and provides us with information on tumor size and shape. The second technique allows imaging of the spatio-temporal distribution of replicating agents (ie, OVs), through the use of artificial peptides presenting magnetic contrast through chemical exchange saturation transfer (CEST). We have thus generated an OV armed with a CEST-reporter gene to be tested in brain tumor oncolytic virotherapy. Because these two technologies can be combined, together they will provide a powerful diagnostic tool to monitor efficacy of OVs and glioma response to virotherapy, thus leading to the design of efficient strategies of virotherapy that overcome the influence of host factors.
P.065. FUNCTIONAL DIFFUSION MAP: NEW IMAGING ASSESSMENT OF GliOBlastOMA PATIENTS TREATED BY BORON NEUTRON CAPTURE THERAPY

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INTRODUCTION: Assessment of therapeutic efficiency for glioblastoma (GB) patients is traditionally accomplished by measuring changes in tumor size on postintratumoral enhanced T1-weighted image at 10 weeks after initiation of treatment. One disadvantage of size measures is the duration for changes to occur, with 10 weeks necessary to assess the response. The functional diffusion map (fDM) which is a new imaging assessment of GB patients was reported by Hamstra et al. This fDM analysis is able to assess at 3 weeks after initiation of treatment earlier than the traditional imaging assessment. In this study, we evaluated GB patients treated by boron neutron capture therapy (BNCT) by using this fDM analysis. MATERIALS AND METHODS: During 2003–2007 period, 17 patients with GB treated by BNCT were retrospectively enrolled onto a study of intratreatment MRI at 2 and/or 7 and/or 14 days, and/or 10 weeks. We used I-Response Tom. 1.0 fDM analysis that is analysis software to be able to assess changes over time of apparent diffusion coefficient (ADC) values. Results and Discussion: The volume of tumor with decrease diffusion analyzed by fDM at 2 days was the strongest predictor of patients survival time since BNCT ($R^2 = 0.7433$). Our study showed that greater decreases in ADC value in response to BNCT over time were observed in the good prognosis patients compared with the poor prognosis patients. The decrease in ADC value in response to BNCT at an acute stage was caused by BNCT as a high-dose radiation therapy, unlike a conventional radiotherapy as a low-dose radiation therapy. Brieﬂy, BNCT might cause tumor cells to swell in an acute stage by the high-dose radiation therapy and fDM analysis captured it as an imaging of fDM. CONCLUSION: The fDM analysis could provide an earlier imaging assessment of GB patients treated by BNCT. Early detection of treatment failure can also allow more intensive therapy in patients with the worst prognoses. This fDM analysis will have the potential to replace size measures. Therefore, we will assess many more the number of GB patients and perform further animal experiments.

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

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CASE REPORT: A 26-year-old male presented with left-sided hearing loss. MRI showed a small, subtle enhancing lesion in the left internal auditory canal (IAC), suggestive of schwannoma. Steroid therapy was started, and the patient was referred and scheduled for surgery in our centre. Two months later, while on the waiting list, the patient noticed right-sided hearing loss. Repeated MRI demonstrated a new right-sided IAC lesion and increased left-sided IAC mass and subtle, bilateral thickening of cranial nerves III–X. Lack of enhancement was attributed to steroid effect. Within the next week, the patient developed progressive cranial nerve deficits. Neither extensive blood, repeated CSF examination, nor PET-CT directed towards inﬂammation or primary malignancy. Biopsy of the IAC-mass was proposed, but declined by the patient. Steroid therapy was continued with vasculitis as working diagnosis and symptoms improved. Twelve months after his ﬁrst presentation, the patient presented with paretic foot musculature. Spinal MRI demonstrated small intradural, nodular/ nodular enhancing lesions in the thoracic spine. The right frontal leptomeningeal deposits. The left temporal lesion was biopsied. Microscopy showed small round blue cells, rosettes, and leptomeningeal proliferation. CD56 immunohistochemical staining conﬁrmed neurogenic origin, Final diagnosis was desmoplastic/nodular medulloblastoma with leptomeningeal deposits. DISCUSSION: Medulloblastoma is the most common pediatric central nervous system malignancy, usually presenting as an intra-axial infratentorial mass. Adult cases are extremely rare (annual incidence 1 per 2–20 million. Leptomeningeal spread occurs in 33% of cases. Extra-axial presentation of medulloblastoma is extremely rare, with only 9 reported cases in literature, the majority presenting as cerebellopontine angle masses. To our knowledge, medulloblastoma presenting as multiple cranial nerve involvement has not been described before.

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

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

Glioblastoma multiforme and anaplastic gliomas

P.069. PROGNOSTIC IMPACT OF STEM CELL MARKER CD133 IN GliOBlastOMA PATIENTS TREATED WITH CONCOMITANT RADIOCHEMOTHERAPY: A PROSPECTIVE STUDY

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Cancer stem cells (CSC) are thought to represent the population of tumorigenic cells responsible for tumor development. The CD133
antigen has been described as a putative stem cell marker in malignant brain tumor that could identify such a tumorgenic population in a subset of glioblastoma multiforme (GBM). To date, the correlation between CD133 expression in primary GBM and patients’ prognosis is not clearly established. To address this question we investigated the relationship between the quantitative expression of CD133 stem cell antigen mRNA using real-time RT-qPCR and patient outcome in a prospective cohort of 61 primary GBM patients treated with radiotherapy combined with concomitant and adjuvant therapy with temozolomide. On multivariate survival analysis, CD133 stem cell antigen expression was a significant (P = .007) prognostic factor for adverse overall-survival independent of extent of resection (P = .012), patient age (P = .037), and MGMT status (P = .021). Furthermore, according to the combined expression of CD 133 and MGMT status, the patients were categorized into three groups. Among these three groups, patients with methylated tumors and low expression level of CD 133 (group I) had the best prognosis. The second more liberal criteria also included cases with stable disease for at least 6 months after first progression. Recurrence was judged unusual occurring contralaterally or extracranially. Tumor status was assessed before and after surgery, 1 month after completion of radiotherapy, and every 3 months thereafter. RESULTS: A total of 136 patients were analyzed, 80 males and 56 females, median age 62 years (17–81), median Karnofsky performance status 75 (20–90). In total, 123 cases were primary GBMs, 13 were secondary, 15 patients had multifocal disease, 69 patients underwent macroscopically complete resection, 40 partial resection, 24 biopsy. 3 had no primary surgery, but were diagnosed by biopsy later. Seventy-three patients were intent to treat with concurrent chemo-therapy followed by 6 cycles of adjuvant TMZ, of which 37 completed the full treatment as planned (50%). Median OS in the combined group was 16 months compared with 8 months in the other group (P = .0003). Pseudo-progression was observed in 10 cases in the combined group (16%) vs none in the other group using the strict criteria (P = .003). Applying more liberal criteria, pseudo-progression was found in 17 cases (27%) in the combined group vs one in the other group (P = .0003). The median time to pseudo-progression was 4 weeks after radiation. Only pseudo-progression assessed by the more liberal criteria was associated with survival (P = .02). An unusual pattern of relapse was observed in 15 (21%) patients who were treated with the combination compared with 6 (10%) in the others (P = .05). CONCLUSIONS: The median OS in the group who received combined therapy was 16 months. Combined treatment is associated with higher incidence of unusual sites of relapse. Contralateral or extracerebral relapses were observed in more than twice as many patients. Pseudo-progression after combined treatment strongly depends on the criteria being used.


BACKGROUND: Combined postoperative therapy with temozolomide (TMZ) has become a standard of care in the treatment of glioblastoma (GBM). Pseudo-progression is often observed since the introduction of this concurrent regimen. The objective of this study is to compare the incidence of pseudo-progression, pattern of recurrence, and overall survival (OS) in patients treated before and after introduction of concurrent TMZ in this indication. METHODS: A retrospective review was conducted of all pathologically proven GBM cases treated postoperatively in our center between 2004 and 2008. OS was calculated from the time of diagnosis. Pseudo-progression was examined by two different criteria. The first strict criteria define pseudo-progression as ≥25% increase in tumor size or the occurrence of a new contrast-enhancing lesion, with, in absence of new active treatment, either subsequent spontaneous regression to baseline or smaller, or pathologically proven tumornecrosis after completion of radiotherapy, and every 3 months thereafter.

RESULTS: A total of 136 patients were analyzed, 80 males and 56 females, median age 62 years (17–81), median Karnofsky performance index at diagnosis 70 (20–90). In total, 123 cases were primary GBMs, 13 were secondary, 15 patients had multifocal disease, 69 patients underwent macroscopically complete resection, 40 partial resection, 24 biopsy. 3 had no primary surgery, but were diagnosed by biopsy later. Seventy-three patients were intent to treat with concurrent chemo-therapy followed by 6 cycles of adjuvant TMZ, of which 37 completed the full treatment as planned (50%). Median OS in the combined group was 16 months compared with 8 months in the other group (P = .0003). Pseudo-progression was observed in 10 cases in the combined group (16%) vs none in the other group using the strict criteria (P = .003). Applying more liberal criteria, pseudo-progression was found in 17 cases (27%) in the combined group vs one in the other group (P = .0003). The median time to pseudo-progression was 4 weeks after radiation. Only pseudo-progression assessed by the more liberal criteria was associated with survival (P = .02). An unusual pattern of relapse was observed in 15 (21%) patients who were treated with the combination compared with 6 (10%) in the others (P = .05). CONCLUSIONS: The median OS in the group who received combined therapy was 16 months. Combined treatment is associated with higher incidence of unusual sites of relapse. Contralateral or extracerebral relapses were observed in more than twice as many patients. Pseudo-progression after combined treatment strongly depends on the criteria being used.

P.071*. CAN OS-6 REPLACE PFS-6 AS A PRIMARY ENDPOINT IN PHASE II STUDIES ON GLIOBLASTOMA PATIENTS GIVEN ANTIANGIOGENETIC DRUGS? E. Franceschi1, A. A. Brandes1, A. Tosoni1, A. Bacchi1, G. Grisi1, F. Spagnolli1, F. Alessandri1, S. Bartoloni1, R. Poggi1, and M. Ermani2,6; 1Medical Oncology Department, Bellaria-Maggiore Hospital, Azienda USL Bologna, Bologna, Italy; 2Neuroradiology Department, Bellaria-Maggiore Hospital, Azienda USL Bologna, Bologna, Italy; 3Radiology Department, Azienda Ospedaliero-Universitaria, Padova, Italy; 4Radiotherapy Department, Bellaria-Maggiore Hospital, Azienda USL Bologna, Bologna, Italy; 5Neuroradiology Department, Ospedale Civile, Verona, Italy; 6Statistic and Informatic Unit, Azienda Ospedaliero-Universitaria, Bologna, Italy

BACKGROUND: In the last decade, progression-free survival at 6 months (PFS 6) has been considered the best endpoint in phase II trials on recurrent glioblastoma (GBM). However, since a “new standard” of care was established by the EORTC/NCIC phase III trial, no data have reported on the PFS-6 or overall survival (OS) obtained with second-line treatment following combined RT/TMZ. Moreover, antiangiogenic agents might alter data on response by repairing the blood–brain barrier and diminishing contrast enhancement, thus precluding the accurate assessment of any reduction in the tumor burden. The issue of a robust primary endpoint for phase II studies is therefore still open. The aim of the study was to evaluate outcome endpoints for second-line treatment at recurrence. METHODS: A retrospective analysis was made using a database on 653 GBM patients followed prospectively between May 2000 and August 2008. A total of 150 patients (median age: 52 years, [24–76 years]) were enrolled. MGMT methylation status, evaluable in 110 patients, was present in 38% of cases. Median OS was 18.5 months. At disease progression, 40 patients (27%) received temozolomide, 92 patients (61%) received chemotherapy-based chemotherapy, and 18 patients (12%) received other treatments. At the time of recurrence, mPFS was 2.5 months (95% CI: 2.0–3.1), PFS-6 15% (95% CI: 9.5%–21.3%), mOS 7.6 months (95% CI: 6.9–8.3) and OS-6 64% (95% CI: 56.6–72.2%). In the Cox proportional hazard model, PFS with the second-line treatment was correlated with OS measured from the start of the second-line treatment (P < .0001).

CONCLUSIONS: The findings made in the present study, the first in literature to evaluate outcome endpoints for a second-line treatment after RT/TMZ in GBM patients, confirm that antiangiogenic drugs combined with OS-6 can be considered as a sound endpoint.

P.072* A PHASE III RANDOMIZED CONTROLLED TRIAL OF SHORT-COURSE RADIOTHERAPY WITH OR WITHOUT CONCOMITANT AND ADJUVANT TEMOZOLOMIDE IN ELDERLY PATIENTS WITH GLIOBLASTOMA MULTIFORME J. R. Perry1, C. J. O’Callaghan2, K. Ding2, A. A. Brandes3, C. Phillips3, J. Menten4, M. Fay5, R. Nishikawa6, C. Winch7, and N. Laperriere8; 1Odette Cancer Center and Sunnybrook Health Sciences Centre, Ontario, Canada; 2National Cancer Institute of Canada Clinical Trials Group, Queen’s University, Kingston, ON, Canada; 3Azienda USL Bellaria-Maggiore Hospital, Bologna, Italy; 4Peter MacCallum Cancer Centre, Melbourne, Australia; 5University Hospital Leuven, Leuven, Belgium; 6Saitama Medical University, Saitama-ken, Japan; 7Princess Margaret Hospital, Toronto, ON, Canada

INTRODUCTION: The EORTC (26981-22981)/NCIC CTG (CE.3) RCT in newly diagnosed GBM found sustained improvement in survival with the addition of concomitant and adjuvant temozolomide (TMZ) to radiotherapy (RT). Study patients were aged 19–71 (median 56 years), and gained 33% improvement in overall survival. A recent RCT in elderly GBM patients found improved survival with RT compared with supportive care alone and another study detected a benefit for 40 Gy/15 vs a 60 Gy/30 RT regimen. Therefore, RT alone is considered standard for elderly patients and 40 Gy/15 is supported as an acceptable fractionation scheme. However, the question remains: does the addition of TMZ to RT confer a survival advantage in elderly patients for whom “short-course” radiotherapy is recommended? Study Design: In order to have 90% power to detect a 33% improvement in the primary outcome of overall survival (increased MST from 6 to 8 months) between arms, using a two-sided 5% alpha, a minimum of 520 deaths must be observed prior to final analysis. Assuming accrual of 150 patients per year, 360 patients will be accrued in 3.7 years with final analysis after 5.7 years. Radiotherapy Department, yielding a study duration of 5 years. Study Progress: The trial is open in Canada (NCIC CTG), Europe (EORTC), Australia and New Zealand (TROG), and Japan. As of March 1 2010, 123 patients were randomized. Median
age is 73 (65–86) years with 78% over the age of 70. Seventy-five percent patients are ECOG PS 0 or 1 and 25% are ECOG PS 2; 69% had sub- or gross-total resection, 31% biopsy only; Discussion: The NCIC CTG CE.6 randomized trial alone vs RT and Adjuvant TMZ is an international cooperative effort addressing an important unmet need in the spectrum of care for newly diagnosed GBM.

P.074*. CIRCULATING ENDOTHELIAL CELLS DECREASE SIGNIFICANTLY IN RELAPSING HIGH-GRADE GLIOMA PATIENTS RESPONDING TO BEVACIZUMAB

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Angiogenesis, the recruitment of new blood vessels, is an essential component of tumor progression. High-grade gliomas (HGGs) are highly vascularized tumors and bevacizumab, a humanized monoclonal antibody targeting the vascular endothelial growth factor (VEGF), is active in preclinical testing in vitro and in vivo. In the clinical setting, in combination with irinotecan, other chemotherapy agents or alone, it has shown significant activity in HGG patients. Therefore, the identification of patients who might benefit from antiangiogenic therapies is crucial for the optimization of treatment strategies. In other solid tumors, levels of circulating endothelial cells (CECs) and circulating progenitor cells (CEPs), contributing to the formation of tumor vessels, correlate with the degree of tumor angiogenesis or the response to angiostatic therapy. Twenty-seven patients with recurrent HGG (22 glioblastomas (GBM) and 5 anaplastic astrocytomas (AA)) were treated at the Neurological Institute C. Besta, Milano, with irinotecan (340 or 125 mg/m² for patients on EIAEDs or not, respectively) and bevacizumab 10 mg/kg every 2 weeks. Median age was 53 years (range 15–66) and median Karnofsky Performance Status (KPS) was 70 (range 50–100). The median number of prior chemotherapy treatments was 2 (range 1–4). Median follow-up was 6 months. Number and viability of CECs and CEPs showed progressive disease in 6 subjects, partial response in 16, and stable disease in 4; 1 patient was lost to follow-up. Overall, 6M-PFS was 50% and 6M-OS was 64%. Median PFS and median OS were 6 and 10 months, respectively. For GBM patients and MFS was 37% and 6M-OS was 65%. At baseline the number of CECs was significantly higher in GBM patients than in AA (113.1 ± 55.7 vs 61 ± 31, P = .04). A significant reduction of CECs and viable CECs was observed only in GBM patients with a clinical and radiological response after 2 months of therapy (11.6 ± 52 vs 70.9 ± 55.3, P = .05 for CECs and 33.4 ± 18.3 vs 16.2 ± 16.4, P = .03 for CECs viable). No significant difference in CEPs number and viability among patients and during treatment was detected. The data suggest that investigations of CEC investigation levels could may contribute to a better understanding of clinical responses to bevacizumab action in HGG patients.

P.075*. THE EXPRESSION OF NG2 IDENTIFIES A TUMOR-COMPETENT POPULATION IN GliOblastoma WITH DISTINCT MOLECULAR SIGNATURE

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INTRODUCTION: We previously demonstrated that NG2 expressing (NG2+) cells in glioblastoma (GBM) exhibits robust proliferative and tumorigenic activity and share phenotypic and functional similarities with NG2 expressing glial progenitors. Here, we conducted comparative studies to address the difference of the molecular signature of GBM-NG2+ and GBM-NG2− cells. METHO Ds: Two mechanisms of tumor heterogeneity were investigated. Stem cell-like cell proliferation was only markedly decreased in cells expressing glial progenitors. Here, we conducted comparative studies to address the difference of the molecular signature of GBM-NG2+ and GBM-NG2− cells. INTRODUCTION: We previously demonstrated that NG2 expressing (NG2+) cells in glioblastoma (GBM) exhibits robust proliferative and tumorigenic activity and share phenotypic and functional similarities with NG2 expressing glial progenitors. Here, we conducted comparative studies to address the difference of the molecular signature of GBM-NG2+ and GBM-NG2− cells. RESULTS: Microarray data indicated that NG2+ cells overexpressed a group of genes previously recognized by Cancer Genome Atlas within the Mitosis and Cell-Cycle Module (MCM). Array data analysis showed overexpression of unique set of proliferative pathways and transcription factors (TFs) by GBM-NG2+ cells. Gene Ontology enrichment identified more than 200 gene categories that were enriched in the GBM-NG2+ cells. The top 10 categories were related to cell cycling, M phase, and DNA replication. Similarly, CGH demonstrated subtle structural differences between the molecular cytogenetic profile of GBM-NG2+ and GBM-NG2−. Finally, we demonstrated that MAPK and Akt pathways were significantly overactivated in GBM-NG2+ compared with GBM-NG2− cells. CONCLUSION: We previously showed the robust proliferative activity and tumorigenesis of GBM-NG2+ cells. Here, we provide evidence that our previous observations are linked to the distinct molecular signature of GBM-NG2+ cells. This signature includes notable structural chromosomal abnormalities, unique enrichment of TFs and MCM genes, and overactivation of MAPK and Akt pathways.

P.076*. NEOADJUVANT TEMOZOLOMIDE FOR GRADE III AND IV ATROCYTOMA: A RANDOMIZED PHASE II STUDY

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BACKGROUND: A pilot study conducted with TMZ given neoadjuvant before radiotherapy (RT) for astrocytoma grade III and IV resulted in long survival times compared with historical controls. We therefore further investigated the value of neoadjuvant TMZ in a randomized phase II trial. During the 6-month period, concurrent radiotherapy became standard treatment and was therefore incorporated in the later part of the trial. MATERIAL AND METHODS: Newly diagnosed patients with astrocytoma grade III (glioblastoma, GBM) or grade III (anaplastic astrocytoma, AA) age ≤60 years and performance status (PS) 0–2 were randomized to receive either 2–3 cycles of TMZ, 200 mg/m² Days 1–5 every 28 days, followed by RT 60 Gy in 30 fractions or RT only. The third TMZ cycle was administered to patients with nonprogressive disease after 2 cycles of TMZ. From June 2005, all patients received TMZ 75 mg/m² daily concomitant with RT. No adjuvant TMZ was given, but was recommended as first-line treatment at progression, unless patients progressed while on TMZ therapy. Primary endpoint was an improved overall survival (OS) compared with historical controls. The primary endpoint showed OS improvement for patients treated with TMZ. From May 2005, all patients received TMZ 75 mg/m² daily concomitant with RT. No adjuvant TMZ was given, but was recommended as first-line treatment at progression, unless patients progressed while on TMZ therapy. Primary endpoint was an improved overall survival (OS) compared with historical controls. The primary endpoint showed OS improvement for patients treated with TMZ. From May 2005, all patients received TMZ 75 mg/m² daily concomitant with RT.
was overall survival and secondary endpoints were safety and quality of life.

RESULTS: A total of 143 patients were enrolled in the trial. Of these 87 (61%) received TMZ concomitant with RT, GBM was diagnosed in 103 patients and AA in 40. Median age was 58 years (range 24–60) and 63% were male. PS was 0–1 for 9.3% of patients and 87% had undergone surgical resection. The treatment arms were well balanced. Of all patients, 71 (50%) were randomized to the neoadjuvant treatment. Of these, 67 (94%) received the first cycle of TMZ, 64 (90%) the second, and 58 (82%) also the third. At the time of data analysis, 98 patients (68.5%) were dead. Median survival time for all patients was calculated to 20.5 months. CONCLUSIONS: The role of TMZ in the treatment of GBM given concomitant with RT and adjuvant is well documented. We explored the value of TMZ given neoadjuvant for 2–3 cycles, before RT for GBM and AA in a phase II randomized trial. The final results will be presented at the upcoming EANO meeting.

P.077*. CANCER STEM CELLS IN Glioblastoma, WHAT ARE THEY?

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P.078. SMALL MOLECULE KINASE INHIBITORS IN Glioblastoma: A Systematic Review of Clinical Studies

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

P.079. NPAS3 IS A NOVEL LATE-STAGE ACTING PROGRESSION FACTOR IN Gliomas WITH TUMOR SUPPRESSIVE FUNCTIONS

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

P.080. A NOVEL METHOD TO ENRICH FOR Glioma STEM CELLS FROM Glioma Cell Lines

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BACKGROUND: Glioma stem cells (GSCs) are inherently similar to stem cells except they can transform into tumors reminiscent of the pathological features of the originated tumor mass. GSCs serve as an excellent pre-clinical model to comprehend tumor re-growth and treatment resistance. Several approaches were previously described to purify GSCs, but seemingly appeared to be laborious, costly, and sometimes with poor yield. Our objective was to investigate alternative strategies to cost-effectively and efficiently enrich for GSCs. METHODS AND RESULTS: We grew 3 glioma cell lines in a serum-free medium to obtain cells with stem cell characteristics from GBM xenografts and determine whether these cells are a subpopulation of the tumor (bonafide GSCs) or represent a changing entity adapting to the signals from the microenvironment. To address this question we apply flow cytometry to identify and characterize small subpopulations of cells within a highly heterogeneous tumor population, according to cell surface and internal markers and according to their drug efflux properties (side population). We have set up an immunodeficient GFP expressing mouse xenograft model, which recapitulates the invasive and angiogenic features of human GBM. The use of a GFP mouse allows to distinguish between tumor and host cells, an important aspect since the invasive and angiogenic features of human GBM. The use of a GFP mouse allows to distinguish between tumor and host cells, an important aspect since the invasive and angiogenic features of human GBM.

P.081. A CHEMICAL GENETICS SCREEN IDENTIFIES NOVEL STEROID INHIBITOR DRUGS THAT INHIBIT THE GROWTH OF Glioma CELL LINES

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BACKGROUND: Gliomas are among the top 5 causes of cancer-related deaths, representing about ~60% of the cases in adults and ~50% in children. Despite current treatments (surgery, radiation, and chemotherapy), the
overall survival is still poor. Current promises exist with patients treated with adjuvant temozolomide; however, only 10%–15% typically have a positive response with combined surgery and radiation therapies leading to prolonged survival of up to 2 years. Since a wide range of steroid receptors are expressed in gliomas, our objective was to investigate whether novel classes of steroid inhibitor drugs can be used efficiently to inhibit glioma growth. To achieve this, we studied the effect of these drugs on the growth of glioma cell lines.

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

**P.082. A CHEMICAL GENETICS SCREEN IDENTIFIES NOVEL STEROID INHIBITOR DRUGS THAT INHIBIT THE GROWTH OF GLIOMA STEM CELLS**

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**BACKGROUND:** Glioma stem cells represent a fraction of cells within a tumor mass that are postulated to be responsible for tumor re-growth. Moreover, recent studies have associated glioma stem cells with impeccable chemoresistance mechanisms, leading to an overall poor survival and failure among patients treated by conventional adjuvant chemotherapy. Since a wide range of steroid receptors are expressed in gliomas, our objective was to investigate whether novel classes of steroid inhibitor drugs can be used efficiently to inhibit glioma growth. To achieve this, we studied the effect of these drugs on the growth of glioma stem cells.

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

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

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**INTRODUCTION:** Brainstem glioma are rare in adults. Literature on the subject is limited to small retrospective studies that described natural course, clinical-radiological presentation, and prognostic factors. Need for histopathological confirmation and therapeutic planning remains controversial. Surgery is first choice when tumor site permits it, even when only subtotal resection can be reached. Nevertheless, radiotherapy is very useful when tumor site permits it and is accessible and can be given to patients with poor clinical condition. Radiotherapy is better tolerable than surgery, has minor complications, and provides acceptable survival. Biopsy might be useful to differentiate with benign processes when MRI is not convincing and to define molecular genetics for future use of targeted agents.

**MATERIAL AND METHODS:** The characteristics of 26 patients aged ≥16 years with brainstem glioma diagnosed in our center between 1987 and 2005 were reviewed. **RESULTS:** The median age at diagnosis is 35 years, with a median survival of 30.1 months (range 4–237.5 months). The main presenting symptoms were cranial neuropathy, ataxia, and/or hydrocephalus. Diagnosis is mostly based on MRI findings. Histological diagnosis was available in only 8 of 26 patients. Contrast enhancement, central necrosis, or poorly delineated lesion on MRI correlate with poor prognosis (median survival of 23.1 vs 120.1 months). Three patients underwent a subtotal resection, but all 26 were irradiated with doses between 51 and 66 Gy. Three patients suffered from radiotherapy-linked complications consisting of necrosis (n = 1) and hearing disability (n = 2). Salvage chemotherapy was given in 5 patients at recurrence with a median survival of 15.7 months. The following patient features (characteristics) predict poorer prognosis: age above 40 years, hydrocephalus, WHO performance above 1 and high grade appearance on MRI. Duration of symptoms <3 months was almost statistically significant to predict poorer prognosis. The more negative prognostic features present, the worse the survival. This was statistically significant. **CONCLUSIONS:** The need to perform a biopsy is a matter of dispute. In our series, contrast enhancement, central necrosis, and poorly marginalized lesions predicted shorter survival, indicating that radiological features can be used to diagnose high-grade glioma including biopsy is not necessary. All patients were irradiated with acceptable survival, only 3 suffered from complications. Radiotherapy alone is still an excellent therapeutic option. Age >40 years, long tracts signs, hydrocephalus, and WHO score >1 predicted for poorer prognosis. Shorter duration of symptoms was almost significant.

This confirms the literature and can be used to decide which patients can benefit from more aggressive treatment. Chemotherapy should be preserved as rescue therapy at recurrence, seeing the median survival in our patient group.

**P.084. GAMMA-KNIFE RADIOSURGERY FOR RECURRENT GlioBLASTOMA RESISTANCE TO THE TEMOZOLOMIDE**

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**PURPOSE:** The current standard of care for newly diagnosed glioblastoma is surgical resection to the extent feasible, followed by radiotherapy plus concomitant and adjuvant temozolomide. Ultimately, despite this current standard treatment, almost all patients with glioblastoma will have relapse. Gamma-knife radiosurgery (GK) stereotactic radiosurgery is a safe and less invasive treatment used as adjuvant therapy for patients with glioblastoma. Several studies have yielded conflicting results in the effectiveness of radiosurgery in glioblastoma. This article describes the results of our institutional experience with GK adjuvant therapy in the treatment of patients with recurrent glioblastoma resistance to the temozolomide.

**METHODS:** Eighteen patients with newly diagnosed glioblastoma were treated with operation and concomitant temozolomide chemotherapy. The median interval between initial diagnosis and treatment was 19.0 months and without GK was 15.0 months. Treatment was well tolerated by all patients. No acute toxicities CTCAE Grade II occurred. Median survival time of patients treated with GK was 19.0 months and without GK was 15.0 months. Treatment was well tolerated by all patients. No acute toxicities CTCAE Grade II occurred. Median survival time of patients treated with GK was 19.0 months and without GK was 15.0 months. Treatment was well tolerated by all patients. No acute toxicities CTCAE Grade II occurred. Median survival time of patients treated with GK was 19.0 months and without GK was 15.0 months. Treatment was well tolerated by all patients. No acute toxicities CTCAE Grade II occurred. Median survival time of patients treated with GK was 19.0 months and without GK was 15.0 months. Treatment was well tolerated by all patients. No acute toxicities CTCAE Grade II occurred. **RESULTS:** Median survival time of patients treated with GK was 19.0 months and without GK was 15.0 months. Treatment was well tolerated by all patients. No acute toxicities CTCAE Grade II occurred. Median survival time of patients treated with GK was 19.0 months and without GK was 15.0 months. Treatment was well tolerated by all patients. No acute toxicities CTCAE Grade II occurred. Median survival time of patients treated with GK was 19.0 months and without GK was 15.0 months. Treatment was well tolerated by all patients. No acute toxicities CTCAE Grade II occurred.

**BACKGROUND:** Clinical outcome of glioblastoma (GBM) patients who receive radiotherapy alone or plus chemotherapy is well established. However, little is known about patients who do not receive this treatment. In published studies, it is difficult to identify the percentage of patients who never receive oncological treatment after surgery and to determine the associated variables. **METHODS:** We reviewed all GBM patients operated in our hospital between January 2000 and December 2008. Patients’ clinical data at our center are prospectively included in a database. We compare those who received oncological treatment and those who did not.
P.086. RECURRENT SPINAL CORD GliOBLASTOMA: SALVAGE THERAPY WiTH BEVACIZUMAB
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BACKGROUND: Primary spinal cord tumors constitute 2%–4% of all primary CNS malignancies in adults of which less than 5% are glioblastoma. A retrospective evaluation to determine toxicity and response to bevacizumab in patients with recurrent spinal cord glioblastoma. PATIENTS AND METHODS: Thirty-five patients (4 males and 2 females; median age 34 years, median survival 21 months) with recurrent spinal cord glioblastoma were treated with bevacizumab (10 mg/kg given once every 2 weeks) and, where tolerated, fotemustine (22 mg/m² given once every 2 weeks). RESULTS: Treatment-related complications included fatigue in 6 patients, constipation in 4, hypertension in 2, thrombocytopenia in 2, and infection without neutropenia in 2. There were 3 grade 3 toxicities (1 each of leucopenia, thrombocytopenia, and hypertension). There were no treatment-related deaths. After one cycle of bevacizumab, 1 patient (17%) demonstrated progressive disease, 2 (34%) partial responses, and 1 (51%) stable disease. Overall median response or stable disease duration (disease free progression) was 7 months (range: 3–11 months). Overall median response or stable disease duration (disease free progression) was 7 months (range: 3–11 months). Overall median response or stable disease duration (disease free progression) was 7 months (range: 3–11 months). Overall median response or stable disease duration (disease free progression) was 7 months (range: 3–11 months). Overall median response or stable disease duration (disease free progression) was 7 months (range: 3–11 months).

CONCLUSIONS: Bevacizumab is well tolerated, has tolerable toxicity, and apparent activity in this small cohort of adults with recurrent spinal cord glioblastoma.

P.087. CONCURRENT 3-TIMES DAILY ULTRACTIONATED RADIATION THERAPY AND TEMOZOLOMIDE FOR NEWLY INOPERABLE GliOBLASTOMA: TEMOFRACT, A PHiSE II STUDY
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PURPOSE: fotemustine is a nitrosourea compound used for the treatment of malignant gliomas, especially in France. Recently, an EORTC-NCIC study has shown that a concomitant combination of radiotherapy plus temozolomide (an oral cytotoxic drug) improved survival in glioblastoma patients. We set out to test a concurrent combination of radiotherapy and fotemustine for newly malignant gliomas. METHODS: A prospective single-centre phase II study opened for accrual in September 2004. Patients over 18 years of age able to give informed consent and with histological proof, newly diagnosed supratentorial malignant gliomas were eligible. All patients were treated by a standard cranial irradiation (conformal irradiation, tumor bulk, a margin of 2.5 cm) and concomitant administration of 10 mg/m² of fotemustine (5 days per week, 6 weeks, 1 hour 30 minutes before radiation therapy). Adjuvant chemotherapy, fotemustine, was administered at tumor progression as standard and classic regimen. RESULTS: Twenty-two patients were enrolled, 16 men and 6 women, median age 56 years (range: 32–74 years), median Karnofsky performance status 70% (range from 60 to 90). Histology included 16 glioblastomas, 3 anaplastic astrocytomas, 2 anaplastic oligodendrogliomas, and 1 mixed glioma. Eight patients underwent surgery (3 total resections) and 14 had a stereotactic biopsy. The concurrent radiotherapy–fotemustine combination was well tolerated: toxicity was mild and 3 hematologic toxicities grade 3–4 were observed. Median survival from initial diagnosis was 9.9 months, 2 patients are currently alive. Median survival was 11 months for surgery and 9 months for stereotactic biopsy. CONCLUSIONS: Concomitant radiotherapy–fotemustine combination is safe and well tolerated. Overall survival of over 10 months for the whole population compares favorably with other reports.

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

P.089. GENE EXPRESSION PROFILING PREDICTS RESPONSE TO TMZ IN GliOBLASTOMAS IN ViTRO
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Glioblastomas are highly lethal neoplasms that cannot be cured which currently available therapies. Temozolomide (TMZ) is a recently introduced alkylating agent that has yielded significant benefits and become a key agent in the treatment of high-grade gliomas including glioblastoma. However, its survival benefit remains unsatisfactory. Understanding the molecular basis of TMZ sensitivity/resistance is necessary for improving the treatment outcome by devising strategies that are able to circumvent primary drug resistance. We therefore combined the in vitro TMZ response with histologic data to identify genes that could potentially be used to predict the response of glioblastomas to
P.090. TEMOZOLOMIDE DOSE DENSE AS SALVAGE TREATMENT FOR GLIOBLASTOMA
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BACKGROUND: There is no clear agreement for the choice of the best second-line regimen after failure of temozolomide standard schedule (TMZ-DD) in patients with recurrent glioblastoma (GBM). In patients with relapsed GBM, dose-dense regimens of TMZ (TMZ-DD) have been applied and the weekly alternating one showed low toxicity and good efficacy. METHODS: We have retrospectively analyzed clinical data of 14 patients treated with TMZ-DD 150 mg/m² 1 week on–1 week off after failure with TMZ-SS in patients with primary GBM. RESULTS: Between July 2007 and January 2010, 14 patients (9 men and 5 women; median age 56; range: 36–72) followed at our institution for primary GBM undergoing TMZ-DD were evaluated. One patient received radiotherapy and radiotherapy (RT) (Stupp regimen); 2 patients received radiotherapy (RT) only (14.3%); 1 for age and 1 for low PS. The treatment outcomes and toxicity were evaluated. RESULTS: The median survival time was 18.5 months. The 1- and 2-year progression-free survival rates were 59% and 20%, respectively. The 1- and 2-year overall survival rates were 74% and 24%, respectively. The high incidence of CSF dissemination was demonstrated as the pattern of recurrence, while the incidence of local recurrence was relatively low. Five patients experienced acute grade 1 toxicities during the treatment. No patients experienced grade 2 or 3 toxicities, including radiation necrosis, cerebrospinal, and intratumoral hemorrhage.

CONCLUSIONS: Our regimen of TMZ with MET-PET contributed to the control of residual infiltrating tumor, resulting in better survival of GBM patients. Survival times in this pilot study are encouraging, and relative favorable result might be from the decreasing of local failure, which suggested that original lesion could be well controlled by high-dose radiation planned by MET-PET. On the other hand, radiation-induced late toxicity was the next problem.

P.091. HYPOFRACTIONATED HIGH-DOSE IRRADIATION PLANNED BY METHIONINE PET FOR THE TREATMENT OF GLIOBLASTOMA MULTIFORME
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PURPOSE: The ability of intensity modulated radiation therapy (IMRT) to deliver a high conformative dose of irradiation to the target has promoted its application studies for patients with glioblastoma multiforme (GBM). Generally, the dose-escalation efforts have relied on the contrast-enhanced MRI, although contrast enhancement is not always an accurate measure of tumor extension. Metabolic imaging studies such as 1H-methionine PET (MET-PET) may improve the ability to identify the target volumes at highest risk of local failure. In this study, we evaluated the clinical significance of hypofractionated high-dose irradiation planned by MET-PET with MET-PET. MATERIAL AND METHODS: Thirty-nine postoperative patients with GBM were treated by IMRT using the tomotherapy system with concurrent chemotherapy. The gross target volumes by MRI (GTV-MRI) and GTV-MET, and CTV was defined as the area including the total volume of GTV-MRI and GTV-MET, and CTV-MET was considered to be that the area of moderate MET uptake, demonstrating a threshold of 1.7 for the standardized uptake value (SUV) of the tumor, compared with that of the normal brain. CTV-MET was considered to be that the area of moderate MET uptake, demonstrating a threshold of 1.3 for the SUV. GTV was finally defined as the area including the total volume of GTV-MRI and GTV-MET, and CTV was defined as the area including the total volume of CTV-MRI and CTV-MET. The GTV and CTV were expanded uniformly by 0.5 and 0.2 cm to generate planning target volumes, PTV-1 and PTV-2, respectively. IMRT was performed in 8 fractions, planning the dose for PTV-1 at 56 Gy and PTV-2 at 40 Gy with concurrent chemotherapy by temozolomide (TMZ) of 75 mg/m² daily. Adjuvant chemotherapy by TMZ of 150 mg/m² was repeated every 4 weeks. At a median follow-up of 13 months, the treatment outcomes and toxicity were evaluated. RESULTS: The median survival time was 18.5 months. The 1- and 2-year progression-free survival rates were 59% and 20%, respectively. The 1- and 2-year overall survival rates were 74% and 24%, respectively. The high incidence of CSF dissemination was demonstrated as the pattern of recurrence, while the incidence of local recurrence was relatively low. Five patients experienced acute grade 1 toxicities during the treatment. No patients experienced grade 2 or 3 toxicities, including radiation necrosis, cerebrospinal, and intratumoral hemorrhage.

CONCLUSIONS: Our regimen of IMRT with MET-PET contributed to the control of residual infiltrating tumor, resulting in better survival of GBM patients. Survival times in this pilot study are encouraging, and relative favorable result might be from the decreasing of local failure, which suggested that original lesion could be well controlled by high-dose radiation planned by MET-PET. On the other hand, radiation-induced late toxicity was the next problem.
any information available on levetiracetam monotherapy. Our results indicate that levetiracetam monotherapy is efficacious in reducing seizures and is well tolerated in the majority of gloma patients suffering from epilepsy.

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

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PURPOSE/OBJECTIVE(S): Elderly patients have largely been excluded from large, randomized trials of therapy for glioblastoma multiforme (GBM). Small randomized trials have been done, evaluating the effect of individual treatment modalities. We reviewed our results of aggressive treatment with surgery, chemotherapy, and radiation in the elderly patients. PATIENTS AND METHODS: From an IRB-approved institutional brain tumor database, we identified patients 70 years of age and older who were newly diagnosed with GBM from May 1979 through September 2007. OS was the primary endpoint of this retrospective study. Univariate and multivariate analyses were performed, utilizing the log-rank test and Cox proportional hazards model to assess the difference in survival for patients with various characteristics and treatment. RESULTS: Two hundred and six patients 70 years of age and older were included in the study. Median OS was 4.5 months. Survival was significantly affected OS included Karnofsky performance status (KPS) (1.8 months for KPS ≤ 50 vs 17.2 months for KPS = 90–100, P < .001); age at diagnosis (3.1 months for age 70–79 vs 3.1 months for age 80 or greater, P < .001); and the extent of disease with patients with bilateral disease (P = .003), multifocal disease (P = .002), and multicentric disease (P = .002) doing worse in all cases. Patients treated with radiation had longer OS of 6.7 vs 1.9 months for those not treated with radiation (P < .001) as did patients treated with chemotherapy who had an OS of 11.2 vs 3.5 months for those not treated with chemotherapy (P < .001). On multivariate analysis, higher KPS (P = .006), surgical resection (P < .001), radiation (P < .001), and chemotherapy (P < .001) were all found to be independently associated with improved OS. CONCLUSIONS: These data suggest that aggressive treatment with radiation, chemotherapy, and surgery improves OS in patients 70 years or older with newly diagnosed GBM.

P.094. TRABEDERSEN IN RECURRENT HIGH-GRAdE GLIOMA: IMPACT ON TUMOR CONTROL AND SURVIVAL

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INTRODUCTION: TGF-β2 regulates key mechanisms of cancerogenesis, namely immunosuppression, metastasis, angiogenesis, and proliferation. The antisense oligonucleotide trabedersen (AP 12009) is a TGF-β2-specific inhibitor and is developed for the treatment of patients with highly malignant tumors such as recurrent or refractory high-grade glioma (HGG). METHODS: Clinical studies with trabedersen in HGG have included 3 phase I/II studies and 1 randomized, active-controlled, open-label, multinational dose-finding phase Ib study. These studies were performed in adult patients with recurrent or refractory HGG (AA, WHO grade III and GBM, WHO grade IV). Trabedersen was administered intratuminorly by convection-enhanced delivery. RESULTS: In the phase Ib study, a total of 145 patients were randomized to either 1 of the 2 doses of trabedersen (10 or 80 μM) or to chemotherapy (TMZ or PCV). One hundred and thirty-four patients (AA = 39 patients, GBM = 95) received study medication during a treat-ment period of about 6 months. In the entire study population, the 10-μM trabedersen group had the highest tumor control rate (CR + PR + SD) at 14 months (22.5% for 10 μM trabedersen vs 6.7% for chemotherapy). The highest efficacy was observed in AA patients treated with 10 μM trabedersen. The proportion of patients showing a response (either CR, PR, or SD) in AA patients was 83% (10 of 12 patients) in the 10-μM trabedersen group, 53% (8 of 15 patients) in the 80-μM trabedersen group, and 58% (7 of 12 patients) in the chemotherapy group. In addition, the duration of response was highest in the 10-μM trabedersen group with 29.1 months compared with the 80-μM trabedersen (24.0 months) and the chemotherapy group (8.0 months). The median time to progression was 22.4 months for the 10-μM trabedersen group and 13.0 months for the chemotherapy group. Furthermore, the 10-μM trabedersen group showed a survival benefit of 17.4 months over chemotherapy (39.1 vs 21.7 months). In addition, promising efficacy data were observed in GBM, especially in patients with age ≤ 55 years and KPS > 80%. Trabedersen generally had a good tolerability and safety profile. CONCLUSIONS: Trabedersen treatment showed a clear clinical benefit in GBM. On the basis of the phase Ib results, the pivotal phase III study SAPPHIRE in patients with recurrent/ refractory AA was started. Patient recruitment is ongoing. Primary endpoint is 2-year survival; secondary endpoints include overall survival, tumor response, quality of life, and safety.

P.095. INCIDENCE AND SURVIVAL IN Glioblastoma Patients WITH PSEUDO-PROGRESSION IN A SINGLE INSTITUTION

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We evaluate incidence and impact in survival and progression-free survival of pseudo-progression (PSP) in patients with glioblastoma (GBM). From December 2006 to September 2009, 61 primary GBM were treated in our institution with resection (54) or biopsy (7) followed by TMZ radiotherapy followed by TMZ (150–200 mg/m²/day for 5 days each 28) for 2 years or until disease progression or unacceptable toxicity. One month after chemo- adiotherapy, MRI was performed and compared with the MRI done within 72 hours after surgery. The 12 and 24 months survival rate and PFS were analyzed by the Kaplan–Meier method, with the use of 2-sided log-rank test statistics. The median age was 50 years (range: 18–72), 43 were males. The median follow-up was 12 month (range: 2–37). The MRI 1 month after the end of radiotherapy showed progressive enhancement in 35 patients (57.3%) and stable disease or minor partial response in 26. All continued with 2 or 3 cycles of temozolomide. Of the 35 patients with progres- sion in the postradiotherapy, MRI 14 (22.9%) had PSP and 21 (34.4%) real early progression (REP). Fifteen of 21 patients (71%) with REP developed new clinical symptoms during or 1 month after radiotherapy but only 4 of the 14 patients (28%) with PSP had new symptoms during this period. PFS was 57% and 21% at 12 and 24 months respectively; the 12 and 24 months survival rate was 59% and 43%, respectively. There was a statistical significant difference in PFS in patients with PSP (P < .0013) and a trend toward better overall survival for patients with PSP but it did not reach statistical significance (P = .08). These data reinforce the notion to con- tinue TMZ in the case of progressive lesions immediately after TMZ radiotherapy. Further research is needed to establish reliable imaging parameters that distinguish between REP and PSP.

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

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Concomitant chemoradiotherapy is a mainstay of treatment for glioblas- toma multiforme; however, all patients progress after the initial treatment. We analyzed treatment our patients received after the progression. Since the introduction of concomitant chemoradiotherapy in the year 2004, we treated 326 patients until the end of 2008. Of those 94 had radiologically demonstrated disease progression and were considered for second-line therapy. Their median age was 53 years (22–78, SD 12.3 years) and after dis- missing disease progression and were considered for second-line therapy. Their median age was 53 years (22–78, SD 12.3 years) and after dis- missing disease progression and were considered for second-line therapy. Their median age was 53 years (22–78, SD 12.3 years) and after dis- missing disease progression and were considered for second-line therapy. Their median age was 53 years (22–78, SD 12.3 years) and after dis- missing disease progression and were considered for second-line therapy. Their median age was 53 years (22–78, SD 12.3 years) and after dis- missing disease progression and were considered for second-line therapy. Their median age was 53 years (22–78, SD 12.3 years) and after dis- missing disease progression and were considered for second-line therapy. Their median age was 53 years (22–78, SD 12.3 years) and after dis- missing disease progression and were considered for second-line therapy. Their median age was 53 years (22–78, SD 12.3 years) and after dis- missing disease progression and were considered for second-line therapy. Their median age was 53 years (22–78, SD 12.3 years) and after dis- missing disease progression and were considered for second-line therapy. Their median age was 53 years (22–78, SD 12.3 years) and after dis- missing disease progression and were considered for second-line therapy. Their median age was 53 years (22–78, SD 12.3 years) and after dis- missing disease progression and were considered for second-line therapy. Their median age was 53 years (22–78, SD 12.3 years) and after dis-
BACKGROUND: Glioblastoma multiforme (GBM) is the most common group of brain tumors in adults with a median survival of only 1 year. A bottleneck in treatment evaluation is that changes in radiologic tumor size are a late effect. Hallmarks of malignant gliomas including tumor vascularity, high cell density, and heterogeneity can indirectly be measured using advanced MRI techniques, such as dynamic contrast enhancement (DCE-MRI), diffusion MRI, and MR spectroscopy (MRS). PATIENTS AND METHODS: Fifteen patients with GBM were included in the study: 10 patients obtaining first-line therapy (radiotherapy + 2 Gy/60 Gy) concomitant with temozolomide (RT/Tmz) and 5 patients obtaining second-line therapy: temozolomide 125 mg/m² concomitant with bevacizumab (Bvz) 10 mg/kg every 14 days. MRS, diffusion MRI, and DCE–MRI were performed at baseline, day 1, 2 weeks, and 6 weeks after treatment start. All measurements were performed with a 1.5 T Siemens Espree. Calculations of apparent diffusion coefficient (ADC) maps were based on a SE–EPI sequence (b-values: 0 and 1000). CSI–MRS was performed using an echo-time of 135 ms. DCE–MRI measurements utilized a pharmacokinetic model to construct parameter maps. V<sub>trans</sub> and V<sub>relax</sub> were calculated. MRSIs at different time points were performed using the Insight registration and segmentation toolkit (ITK) implemented in a Matlab<sup>®</sup> environment.

RESULTS AND DISCUSSION: In general, following observations were made: with pronounced inter-individual differences. MRS: In patients treated with RT/Tmz, there was a steady decrease of the Cho/NAA and the Cho/Chr ratio which persisted during the treatment period and was detected as early as 2 weeks after treatment start. The decline was more pronounced during the first 2 weeks than the rest of the 6-week course. DIFFUSION MRI: An increase in mean ADC values could be visualized at day 1, and this gradual increase persisted during the 6-week follow-up. DCE–MRI: In patients treated with Bvz/Tmz a clear decrease in K<sub>e</sub> and V<sub>relax</sub> could be seen after only 3 weeks of treatment with DCE–MRI, indicating a decrease of vascular permeability and leakage respectively. CONCLUSIONS: Important surrogate markers for angiogenesis, diffusion, and cell density tend to assume a more "normal" pattern after a very short treatment period in a series of patients. Studies with the objective to expand the number of patients and correlate these findings to patient outcome are ongoing at our department.

P.097. THE USEFULNESS OF MS-MLPA FOR DETECTION OF MGMT PROMOTER METHYLATION IN THE EVALUATION OF PSEUDO-PROGRESSION IN GliOBLASTOMA PATIENTS

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We investigated the usefulness of the methylation-specific multiplex ligation probe amplification (MS-MLPA) designed for evaluating semi-quantitative 6-methylguanine DNA methyltransferase (MGMT) promoter methylation status to diagnose the pseudo-progression, which is a major diagnostic dilemma in modern treatment protocol involving concurrent chemoradiotherapy in malignant gliomas. Methylation ratio of promoters of MGMT and mismatch repair (MMR) genes and their copy number variation is assessed by MS-MLPA on 24 samples of glioblastoma patients. The results were compared with those of methylation-specific polymerase chain reaction (MSP) and the protein expression of genes. The correlation between those molecular data and clinical outcome was analyzed. In case of radiological progression after chemoradiotherapy, the sensitivity and specificity of the MS-MLPA were 100% and 75% which was better than MSP in the decision of pseudo-progression using cut-off value of 0.2 for methylation ratio and 0.8 for copy number ratio. MS-MLPA result of MGMT gene was well correlated with those of MSP and IHC staining while there was insignificant correlation between MSP and IHC staining. MMR genes had little variability in promoter methylation and their protein had homogenous tissue expression. We conclude that MS-MLPA is a useful method for the early detection of pseudo-progression in glioblastoma patients.
Abstracts

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

P.101. MALIGNANT GLIOMA SURGERY IN ELOQUENT BRAIN AREAS
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OBJECTIVES: The surgical studies have demonstrated that the extent of anaplastic glioma resection is significantly correlated with patient median survival. The goal of glioma surgery adjacent to eloquent areas remains a procedure with high-level postoperative neurological disorders as a result of wide tumor infiltration of functional cortex and subcortical pathways. Accurate preoperative and intraoperative identification of the eloquent cortex is an essential advantage of surgical excision of gliomas involving motor and speech area. METHODS: A total of 36 patients (21 males, 15 females, mean age 48.3 years, range 21–70 years) who underwent resection of cortical or subcortical tumors located within or close to motor areas have been included. The operation was done under neuronavigation (6 CT, MRI, fMRI, SPECT, and computed EEG studies. Brain tumors located in eloquent area in 21 patients (motor area in 12 cases, sensory area in 9 cases) and in close to eloquent area in 15 patients (motor area in 3 cases, sensory area in 7 cases). Tumor microsurgery was also carried out using the StealthStation navigation system accompanied with intraoperative laser thermodestruction (808 nm, 18 W). RESULTS: Sixteen patients had glioblastoma multiforme and 20 had anaplastic astrocytoma. A gross total or nearly gross total tumor resection was accomplished in 19 patients, and subtotal resection was carried out in 17 patients. Neuronavigation technology helped to define the radiographic limits of the tumor, to perform preoperative planning and minimal access craniotomy. The intraoperative orientation by connection of an anatomical and functional landmarks allowed performing image-guided tumor excision beyond functional zones with maximal extension of tumor resection volume. Laser thermodestruction of residual tumor parts was used after microsurgical tumor removal in regions around sensorimotor and speech areas. Laser thermodestruction increased the rate of complete citoreduction and performed an aimed coagulation without traumatization of eloquent cortex. CONCLUSIONS: The gross total resection of anaplastic gliomas could be performed in eloquent brain regions with an acceptable level of motor and speech impairment. The improved preoperative neuronavigation mapping, intraoperative neuronavigation technique with laser thermodestruction allow maximal safe resection of tumor that predict higher levels of quality of life in patients with brain gliomas in eloquent area.

P.102. NEAR-CONTINUOUS TEMOZOLOMIDE AND LOW-DOSE WEEKLY CCNU: A NOVEL CHEMOTHERAPY REGIMEN WITH ACTIVITY IN MALIGNANT GLIOMAS RESISTANT TO DOSE-DENSE TEMOZOLOMIDE ALONE
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BACKGROUND: Alkylating chemotherapy with CCNU is active in recurrent malignant glioma, but may be antagonized by anti-alkylating MGMT. OBJECTIVES: The optimal treatment for elderly patient with glioblastoma remains controversial. The aim of this study was to verify the activity and the toxicity of temozolomide (TMZ) administration concurrent and adjuvant to radiotherapy in elderly patients with glioblastoma (GBM), and to explore correlation between clinical outcome and O(6)-methylguanine-DNA-methyltransferase (MGMT) promoter methylation status. PATIENTS AND METHODS: From April 2006, 23 consecutive newly diagnosed GBM patients aged 65 years or more (median age 72 years) and a KPS of ≥ 70 were treated with radiotherapy (total radiation dose 60 Gy) and TMZ for 6 months. RESULTS: Nine of the 11 patients with MGMT promoter methylated status had a better survival. However, the survival in patients with MGMT promoter unmethylated status was comparable with patients having MGMT promoter methylated status. CONCLUSIONS: Radiotherapy plus concomitant and adjuvant TMZ was well tolerated with an acceptable rate of toxicity, and patients with a MGMT promoter methylated status had a better survival. However, further prospective trials are needed to confirm these results.

P.103. RADIOTHERAPY PLUS CONCOMITANT AND ADJUVANT TEMOZOLOMIDE FOR GliOBlastoma in ELDERLY PATIENTS
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OBJECTIVES: The optimal treatment for elderly patient with glioblastoma remains controversial. The aim of this study was to verify the activity and the toxicity of temozolomide (TMZ) administration concurrent and adjuvant to radiotherapy in elderly patients with glioblastoma (GBM), and to explore correlation between clinical outcome and O(6)-methylguanine-DNA-methyltransferase (MGMT) promoter methylation status. PATIENTS AND METHODS: From April 2006, 23 consecutive newly diagnosed GBM patients aged 65 years or more (median age 72 years) and a KPS of ≥ 70 were treated with radiotherapy (total radiation dose 60 Gy) and TMZ for 6 months. RESULTS: Nine of the 11 patients with MGMT promoter methylated status had a better survival. However, the survival in patients with MGMT promoter unmethylated status was comparable with patients having MGMT promoter methylated status. CONCLUSIONS: Radiotherapy plus concomitant and adjuvant TMZ was well tolerated with an acceptable rate of toxicity, and patients with a MGMT promoter methylated status had a better survival. However, further prospective trials are needed to confirm these results.

P.104. SAFETY ANALYSIS OF RANDOMIZED BELGIAN PHASE II TRIAL OF EXTENDED USE OF ADJUVANT TEMOZOLOMIDE IN NEWLY DIAGNOSED GliOBlastoma PATIENTS
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PURPOSE: We conduct a Belgian randomized phase II trial to determine whether prolonged administration of temozolomide (TMZ) in newly diagnosed GBM patients increases their progression-free survival (PFS). We also assess the safety profile of this extended use of TMZ since no data are available yet. METHODS: Patients with newly diagnosed glioblastoma presenting with a response or stable disease after the standard treatment of 6 months adjuvant TMZ, were included. These patients were randomized between continued treatment with TMZ or observation, using residual tumor and MGMT status as stratification factors. Patients randomized in the observation arm were rechallenged with TMZ upon progression. We will report here the PFS at 6 months and the safety analysis from the interim analysis. RESULTS: The first 20 patients included were comparable between both arms in terms of the well-known prognostic factors such as median age at diagnosis 55 vs 56 years, Karnofsky score 84 vs 92%, residual tumor in 8 vs 9 patients, and steroids use for 5 vs 2 patients in prolonged TMZ arm and observation arm, respectively. The progression-free survival (PFS) at 6 months was 70% vs 57%, respectively. The median number of cycles was 6 in the prolonged TMZ arm. Three patients presented with a complete response after 6 months of added TMZ. The mean number of all continuously, enabling a gradual dose adaptation. Hematological WHO grade III + IV toxicity occurred in 5 of 11 patients (45%), 2 of them were symptomatic. One patient had a prolonged elevation of liver enzymes which improved partially after termination of levetracetam. Best response after ≥ 2 months were: 1 complete and 2 partial remissions (27%), 3 stable diseases (27%), 5 progressive diseases (46%). Median overall survival after start of chemotherapy was 4.5 months, progression-free survival at 6 months (PFS6) was 18%, overall survival at 6 months 23.5 months. CONCLUSIONS: In spite of adverse prognostic signs, the objective remissions indicate activity of combined near-continuous temozolomide and low-dose weekly CCNU after failure of dose-dense temozolomide alone. Hematotoxicity, though, has to be controlled vigorously. The results have to be controlled in a larger, prospective series.
grade toxicity per patient was 3.5 (+ 3.3). The toxicities of TMZ were, in the majority of cases, limited to grade 1–2; 4 patients had an asymptomatic grade 3 lymphopenia, 3 had grade 3 asymptomatic thrombocytopenia, and 1 patient had grade 3 anemia. But only 1 patient in this arm had to stop TMZ because of hematological toxicity. In the observation arm, 5 patients were rechallenged and 3 cycles were given without any response. Patients presented with grade 1 toxicity and only 1 patient had a grade 2 toxicity. Patients were able to finish the concomitant therapy - the majority of patients had to stop temozolomide in the prolonged adjuvant TMZ arm but only 1 patient had to stop treatment. This analysis shows a potential benefit of the experimental arm in terms of PFS at 6 months. Accrual is nearly completed and updated results on safety will be reported.

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

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Vaults are highly conserved ribonucleoprotein particles containing a small untranslated RNA (vrRNA). The 110-145 kDa major vault protein (MVP) has been implicated in the regulation of multiple cellular processes, including transport mechanisms, chemoresistance, and several signaling cascades/molecules (eg, MAPK and PI3K pathway). While in normal brain the expression of MVP is very low, MVP expression is consistently upregulated in gliomas including glioblastoma multiforme (GBM). Aim of this study was to investigate whether MVP/vaults have an impact on GBM cell growth and aggressiveness, including chemotherapy responsiveness and to clarify underlying molecular mechanisms. MVP and MVP–GFP fusion proteins were overexpressed by plasmids and adenoviral constructs. Endogenous MVP expression was repressed by shRNA. Protein expressions were detected by immuno-fluorescence and Western blot. Consequences of MVP modulation on cell proliferation, migration, and invasion capacities were analyzed by growth curves, scratch and transwell-chamber assay, respectively. Moreover, tumor formation in dependence of MVP expression was tested in SCID mice. Ectopic MVP expression in MVP-negative H7 glioma cells led to a significantly enhanced proliferative and migratory potential in vitro. Especially responsiveness to epidermal growth factor (EGF)-mediated growth stimulation was increased parallelly by significant upregulation of MAPK and PI3K pathway indicated by phosphorylation of ERK and AKT, respectively. Accordingly, several signal mediators of these pathways, including PTEN and p53, were detected in immunoprecipitates from MVP-overexpressing cell clones. MVP transgenic cells were significantly resistant to cell death induced by serum-starvation but only marginally protected against the cytotoxic effects of diverse chemotherapeutics. Expression of a truncated MVP molecule harboring only the MVP coiled-domain and/or MVP down-modulation by shRNA in MVP-positive GBM cells induced programmed cell death in a caspase-dependent manner, respectively. We also demonstrated that tumor growth in SCID mice was significantly enhanced in all MVP overexpressing H7 subclones when compared with vector controls. Our data prove a significant contribution of vaults/MVP to the malignant phenotype of human GBM cells as supporting activation of oncogenic signaling pathways and growth/survival factor responsiveness.


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

P.108. UPDATED RESULTS OF A PHASE II TRIAL OF BEVACIZUMAB AND IRINOTECAN IN RELAPSED HIGH-GRADE GLIOMA

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BACKGROUND: Relapsed glioblastoma multiforme (GBM) has a poor response to current chemotherapy and prognosis of patients with recurrent disease is dismal, with a median survival of 3–6 months. Numeral trials using bevacizumab, a humanized IgG1 monoclonal antibody to vascular endothelial growth factor (VEGF), with or without chemotherapy, have reported excellent response rates using 10 mg/kg or 15 mg/kg every 2 weeks, and allowed expedite FDA approval for its use as a second-line treatment in relapsed GBM. We performed a phase II trial of bevacizumab using 5 mg/kg only, with irinotecan (CPT 11) every 2 weeks as reported in the initial presentation by Stark Vance. In our interim analysis, we had demonstrated excellent response rates and similar results to others. This is an update of the final results. PATIENTS AND METHODS: This phase II trial accrued 30 patients with recurrent GBM who received bevacizumab at 5 mg/kg and CPT 11 at 125 mg/m2 every 2 weeks, after failing radiation therapy and adjuvant TMZ. All patients on antiepileptic drugs (AEDs) had their regimen changed to nonenzyme-inducing antiepileptic drugs (NEIAEDs) prior to receiving CPT 11. Patients with KPS ≥ 50% were allowed regardless of prior relapses. Patients were evaluated clinically and with contrast-enhanced MRI scan every 4 treatments of bevacizumab until progression. RESULTS: All 30 patients were evaluable. Responses were assessed radiographically according to the MacDonald criteria and comparing T2 or Flair weighted Sequences; 19 patients (63%) had a documented response (CR + PR), 6 patients (20%) had stable disease (SD) and 5 patients (19%) progressed (PD). The average number of bevacizumab treatments received was 5.6 (1–20). The 6-month progression-free survival was 33.4%; 6-month overall survival was 66.7%, median overall survival was 8.7 months (36.3 weeks); median progression-free survival was 5 months (22.5 weeks). Several complications were reported: 3 DVT’s and 2 PEs requiring IVC filter placement, 2 intracranial hemorrhages and 1 pneumonia. Finally, 3 patients died of a catastrophic complication. All patients had bevacizumab and were taken off steroids rapidly after starting bevacizumab regardless of radiological response. Clinical and radiographic responses correlated well. Failures were mostly local progression in 12 cases, and radiological nonenhancing (glioma-like) in 10 cases and multifocal including subependymal and leptomeningal in 8 patients. CONCLUSION: Bevacizumab-based regimen for relapsed GBM demonstrates superior activity when compared with historical treatments. It is safe and improves overall quality of life in this patients’ category. Our results were as promising as previously described, despite lower KPS on enrollment, and using lower doses of bevacizumab.
P.109. EARLY INITIATION OF RADIOTHERAPY PLUS CONCOMITANT AND ADJUVANT TEMOZOLOMIDE (TMZ) AND OVERALL SURVIVAL (OS) IN GLOBLASTOMA (GBM) PATIENTS

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OBJECTIVE: The influence of early start of radiotherapy plus concomitant and adjuvant temozolomide on overall survival (OS) in GBM patients was retrospectively investigated. METHODS: Forty-eight consecutively histologically verified glioblastoma patients (median age 62.5 years, from 25 to 82, 19 females and 29 males, WHO performance status 0–1) received surgery (15 biopsy, 18 partial, and 14 complete resections) and radiotherapy (start median 17.5 days, from 12 to 27 days after surgery) with concomitant and adjuvant TMZ (all patients completed 60 Gy in 2 Gy/day fractions, 5 day/week, 40 of 46 completed concomitant TMZ, 18 of 40 additionally 6 cycles of adjuvant TMZ). No significant wound complications leading to revision surgery occurred. RESULTS: Altogether, the 12 of 24 month OS was 54/20.2% with a median survival of 13.7 months. In younger patient (<65 years, median 75.5, 28 patients), the 12 of 24 month OS was 68/34.3% with 16.9-month median survival, in older patient (>65 years, median 73, 20 patients) the 12 of 24 month OS was 28.8/5.8%, with 7.7-month median survival (Log-rank, P = .0005). The OS comparing RT start <16days with >16days was not significantly different. Extent of surgery influenced OS in the young age group (biopsy vs complete: P = .06), but not in patients ≥65 years (P = .5). CONCLUSION: As the 12 of 24 month OS in our patients ≤65 years has a 57 years OS similar to that of the OS of the EORTC study (61.1/26.5%) with comparable demographics except for therapy start (EORTC median 3 weeks), we speculate that early start of the RT/TMZ might be of additional benefit.

P.110. PHASE II STUDY OF IFOFOSAMIDE, CARBOPLATIN, AND ETOPOSIDE IN PATIENTS WITH A FIRST RECURRENTNESS OF GLOBLASTOMA MULTIFORME

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OBJECTIVE: The prognosis of recurrent glioblastoma multiforme (GBM) remains unsatisfactory. The authors conducted a Phase II study of ifosfamide, carboplatin, and etoposide (ICE) for a first recurrence of GBM to determine whether it prolongs a patient’s good quality of life. METHODS: This trial was an open-label, single-center Phase II study. Forty-two patients with a first GBM relapse after surgery followed by standard radiotherapy (60 Gy) and first-line temozolomide- or nimustine-based chemotherapy were eligible to participate. The primary endpoint was progression-free survival at 6 months after the ICE treatment (PFS-6), and secondary endpoints were response rate, toxicity, and overall survival. Chemotherapy consisted of ifosfamide (1000 mg/m2 on Days 1, 2, and 3), carboplatin (110 mg/m2 on Day 1), etoposide (12 mg/m2 on Days 1, 2, and 3), every 6 weeks. RESULTS: Progression-free survival at 6 months after ICE treatment was 35% (95% CI 22–50%). The median duration of PFS was 17 weeks (95% CI 10–24 weeks). The response rate was 25% (95% CI 9–43%). Adverse events were 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.111. LONG-TERM SURVIVORS OF GLOBLASTOMA

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

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

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Glioblastoma multiforme (GBM) is the most common form of malignant brain cancer in adults. Patients with GBM have a uniformly poor prognosis, with a median survival of 1 year thus advances on all scientific and clinical fronts are needed. We have developed a human glioblastoma xenograft model in nude rodents that is characterized by a highly infiltrative nonangiogetic phenotype. Upon serial transplantation, this phenotype will develop into a highly angiogenic tumor. Thus, we have developed an animal model where we are able to establish two characteristic tumor phenotypes that define human glioblastomas (ie, diffuse infiltration and high neovascularization). It is well established that the cancer genome is molded by the dual processes of somatic mutation and selection. In order to assess whether the observed phenotypic shift is because of clonal selection in vivo, we have performed high-resolution aCGH on primary tumors and xenografts derived thereof. We show that although the overall genomic pattern is highly conserved, additional genomic events trigger the switch from an invasive to a highly angiogenic phenotypic observed in vivo. We are currently further analyzing our findings by applying whole exome sequencing to the analyzed samples to delineate the mutational evolution of xenografted gliomas at single-nucleotide resolution and identify new mutational events linked to the phenotypic switch. This molecular dissection of the 2 hallmarks of GBMs could lead to the identification of potential biomarkers that facilitate the elucidation of the molecular pathways involved in the switch from invasive to angiogenic growth, thereby potentially opening new diagnostic and treatment avenues in the clinic.
P.114. IDENTIFICATION OF CD133+/TELOMERASeLOW PROGENITOR CELLS IN GlioBLASTOMA-DErIVED CANcer STEM STELL LINES

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Glioblastoma multiforme (GBM) is paradigmatic for the investigation of cancer stem cells (CSC) in solid tumors. The CSC hypothesis implies that tumors are maintained by a rare subpopulation of CSC that gives rise to rapidly proliferating progenitor cells. Although the presence of progenitor cells is crucial for the CSC hypothesis, progenitor cells derived from GBM CSC are yet uncharacterized. Our data suggest that in the subgroup of CD133+ primary astrocytic GBM, CD133+/telomerase− CSC give rise to non-tumorigenic, CD133−/telomerase− progenitor cells. The progenitor cell population proliferates rapidly resulting in significant telomere shortening when compared with the CD133+ compartment comprising CSC. The average difference in telomere length as determined by a modified multi-color flow FISH (fluorescence in situ hybridization) was 380 bp corresponding to 4–8 cell divisions. Taken together, we demonstrate that CD133+ primary astrocytic GBM comprise a rapidly proliferating, CD133−/telomerase− low progenitor cell population in addition to CSC and terminally differentiated cells.

P.115. BEVACIZUMAB FOR THE TREATMENT OF PATIENTS WITH RECURRENT HIGH-GRADE GLIOMA, RESULTS FROM A DUAL-CENTER CLINICAL EXPERIENCE IN BELGIUM

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BACKGROUND: Vascular endothelial growth factor (VEGF) plays a key role in the neo-angiogenesis that characterizes high-grade gliomas (HGG). Bevacizumab (BEV), a humanized immunoglobulin G1 monoclonal antibody that inhibits VEGF, has demonstrated activity against recurrent HGG. PATIENTS AND METHODS: Patients with progressive HGG following prior standard care (including at least surgery, radiotherapy, and temozolomide) who received BEV (at a dose of 10 mg/kg every 3 weeks or 15 mg/kg every 3 weeks) outside a clinical trial protocol were identified in 2 Belgian university hospitals. Tumor response and anti-edema effect were determined by magnetic resonance imaging (MRI, including T1- and T2-weighted images associated with stability or reduction on FLAIR). A reduced uptake of amino-acid tracer on PET scan was documented in 3 of 4 patients at the time of this analysis of the off-study use of BEV for recurrent HGG, activity and tolerability were comparable with what has been reported from prospective phase II trials. A meaningful subgroup of patients in this series derived a durable treatment effect with evidence for a metabolic response in addition to an edema reducing effect.

P.116. FUNCTIONAL VALIDATION OF NOVEL MOLECULAR TARGETS FOR ANTI-ANGIOGENIC TREATMENT OF MALIGNANT GLIOMAS

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Glioblastoma multiforme (GBM) remains one of the most malignant tumors in mankind. Despite a multimodal treatment, prognosis and survival of patients remain poor. The highly angiogenic properties of GBM makes anti-angiogenic therapy an attractive addition to the current treatment protocol. Our group is currently active in identifying and characterizing novel biomarkers and therapeutic targets involved in the angiogenic switch observed in malignant gliomas. Making use of a clinically highly relevant xenograft model that recapitulates the invasive and angiogenic properties of GBM within consecutive generations of rats, we have previously performed a large-scale iTRAQ-based proteomics study comparing nonangiogenic to angiogenic GBM phenotypes. From more than a thousand quantifiable proteins identified in membrane fractions, about 120 proteins showed increased expression in angiogenic gliomas. Known and novel candidate-apt proteins have been identified. On the basis of their expression profile and established literature knowledge, we have selected a dozen of proteins for which the differential expression in angiogenic gliomas was validated by quantitative PCR. For functional analysis, we are currently targeting these genes using small interfering RNAs (siRNA) to specifically knockdown the proteins in various glioma cell lines, including glioma stem-cell-like cells. The transfected cell lines are analyzed with regard to their proliferation rate, migration capacity, invasiveness, and clonogenic potential. Tube formation in siRNA-treated HUVEC endothelial cells is measured to evaluate the effect of the proteins on angiogenesis. Complementary data are obtained by overexpression studies of the selected proteins. We will report on the functional involvement of new candidate proteins in glioma angiogenesis, which may represent novel molecular targets for the development of anti-angiogenic therapy in the management of GBM.

P.117. BEVACIZUMAB AND FOTEMUSTINE AS SALVAGE THERAPY IN RECURRENT GLIOBLASTOMA: A PHASE II MULTICENTER ITALIAN STUDY

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BACKGROUND: Recent evidence indicates that antiangiogenic therapies have an important role in recurrent high-grade gliomas. Bevacizumab, a humanized monoclonal antibody against vascular endothelial growth factor (VEGF), has been reported to be active with acceptable toxicity. We report the preliminary results of a multicenter open-label phase II study on bevacizumab plus fotemustine in GBMs recurrent after standard treatment (surgery, radiation, and temozolomide). PATIENTS AND METHODS: Fifty-nine patients (38 males and 21 females) with a median age of 58 years (range 24–78), and a median KPS of 80 (range 60–100) were enrolled in a phase 2 protocol with bevacizumab at 10 mg/kg on day 1, 15 and fotemustine at 75 mg/m²/day on day 1, 8 (induction phase) and, after 3 weeks interval, bevacizumab at 10 mg/kg and fotemustine at 75 mg/m² every 3 weeks as a maintenance. Treatment was maintained until tumor progression or unacceptable toxicity. MRI was performed at baseline, after the induction phase and thereafter every 2 months. Response was defined as a reduction of enhancement on T1-weighted images associated with stability or reduction on FLAIR images (according to recently modified Macdonald’s criteria). Primary end-point was 6-month progression-free survival, whereas secondary endpoints were response rate, overall survival, and safety. RESULTS: The 6-month progression-free survival was 32% and median survival time was 6.7 months (range 1.2–18.4). The overall response rate was 43.4%, with 43.4% complete responses, 8.6% major partial responses, 30.5% partial responses, and 41% stabilization. Maximal responses were precocious, after the induction phase. Steroids were reduced or stopped in 61% of...
Patients. Forty percent of responders had unmethylated MGMT promoter. The most frequent side effects were: hematological grade 3–4 toxicity (21%); fatigue (46%); mild arterial hypertension (9%); and one grade III hypertension with reversible hypertensive encephalopathy; hemorrhagic events (12.5%) (2 lobar hemorrhages, 2 asymptomatic intratumoral bleedings, 1 esophageal bleeding); thrombotic events (9%) (1 pulmonary embolism, 2 TVP, and 1 stroke); mild proteinuria (14%). CONCLUSIONS: Bevacizumab in combination with fotemustine was well tolerated and active in recurrent glioblastoma. The correlations between MGMT status, MRI perfusion, and response is ongoing.

P.118. RADIOTHERAPY AND CONCOMITANT AND ADJUVANT TEMOZOLOMIDE: TRANSLATION OF RANDOMIZED CONTROLLED CLINICAL TRIAL EVIDENCE INTO ROUTINE CLINICAL PRACTICE
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INTRODUCTION: Glioblastoma multiforme is the commonest primary malignant brain tumor in adults, and is usually rapidly fatal. Until 2004, standard treatment in the UK comprised of maximal surgical debulking followed by radiotherapy. The most important advance in recent years has been the addition of concomitant and adjuvant temozolomide, which has been shown to improve overall survival in this group of patients. In addition, data have demonstrated differing outcomes for patients treated with temozolomide depending on the methylation status of the promoter region of the gene for methyl guanine methyl transferase (MGMT) within tumor tissue. MGMT is a DNA repair enzyme that may repair sublethal damage because of alkylating agents. Methylation of the promoter region of the gene may decrease levels of the enzyme in tumor tissue, with a consequent increase in cytotoxicity. METHODS: Trial patients often represent a highly selected group. We undertook a retrospective review of all patients with glioblastoma multiforme treated with concomitant temozolomide at our center between June 2005, when temozolomide was licensed in the UK for this indication, and December 2007. CONCLUSION: We demonstrate close correlation between our outcomes at a minimum follow up of 2 years with those seen in the sentinel trial. In addition, patients were assessed for tumor methylaton status and again we demonstrate close correlation with published data. This clinical audit confirms that the benefit of this regimen can be translated into routine clinical practice within the National Health Service.

P.119. TREATMENT WITH MULTIKINASE INHIBITOR SORAFENIB FOR RECURRENT CENTRAL NERVOUS SYSTEM TUMORS
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OBJECTIVES: Treatment for recurrent central nervous system (CNS) tumors is limited. The multitkina inhibitor sorafenib induces apoptosis and blocks cell proliferation in a variety of tumors and cell lines. The response rate and safety was evaluated in a pilot series. PATIENTS AND METHODS: Twenty patients (3 women and 17 men) with recurrent CNS tumors received sorafenib 200 mg twice daily. The median age was 48 years (range from 23 to 65 years). Seven patients presented with GBM, 6 with anaplastic astrocytomas, 2 with ependymomas, 3 had meningiomas, 1 hemangioblastoma, and 1 hemangioendothelioma. All patients had previously received more than two lines of systemic treatment. RESULTS: Two (of 7) patients with GBM had partial remission (PR), lasting for 3–5 months, stable disease (SD) was observed for 2–7 months in 4 cases. One patient showed clinical and radiological progress (PD) 5 weeks after treatment start. Regarding anaplastic astrocytomas, 4 (of 6) patients showed SD for a time period of 2–9 months. Partial response in 2 patients was lasting for 5 months. In ependymomas, 1 PR (9 months) and 1 SD (8 months) was observed. Patient with hemangiopericytoma has still an SD for more than 5 months. In ependymomas, 1 PR (9 months) and 1 SD (8 months) was observed. One patient with hemangioblastoma had stable disease (SD) for 2–7 months in 4 cases. One patient with hemangioblastoma showed a progressive disease. The best-achieved response within meningiomas was SD (1/3) for 6 months. Median time to progression for all patients was 3.5 months. Dose reduction was necessary in all patients mostly because of hypertension that was controlled with angiotensin-converting enzyme inhibitors or with antihypertensive combination therapy. More than 10 patients had skin changes similar to hand-foot syndrome grade II–IV. One gastrointestinal bleeding was reported, but no origin of hemorrhage was found. Some patients reported episodes of diarrhea which in one case lead to treatment discontinuation. Deep venous thrombosis was not observed in our patient cohort. CONCLUSION: Multikinase inhibitor sorafenib showed responses in heavily pretreated patients with recurrent CNS tumors.

P.120. ACTIVATION OF P53 BY MDM2 ANTAGONISTS DOWN-REGULATES SURVIVIN AND INDUCES CELL-CYCLE ARREST AND APOPTOSIS IN HUMAN GLOBLASTOMA MULTIFORME
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Glioblastoma multiforme (GBM) is the most common and aggressive primary brain tumor in adults. Despite concerted efforts to improve current therapies and develop novel clinical approaches, patient survival remains poor, owing to the resistance of glioma cells to classical chemotherapies. Consequently, new classes of drugs, including small-molecule antagonists of MDM2, have been developed to inhibit the p53–MDM2 interaction and activate p53 signaling in cancer cells. We investigated whether nutlin-3a might be effective in inducing apoptosis in GBM. Glioma cell lines and primary cultured glioblastoma cells with known TP53 status were treated with nutlin-3a, and inhibition of cell growth and apoptosis induction were evaluated. Upon treatment with MDM2 antagonists, p53-dependent G2-M cell cycle arrest and apoptosis were effectively induced in p53−−wild-type glioma cell lines. Nutlin-3a induced down-regulation of Survivin mRNA and protein expression together with up-regulation of PUMA mRNA and p21 and PUMA protein induction. In wild-type TP53 primary cultured glioblastoma cells, nutlin-3a induced p53-dependent suppression of Survivin, overexpression of PUMA and/or Noxa protein and apoptosis. Primary cultured glioblastoma cells and glioblastoma cell lines with mutant p53 or functionally impaired p53 pathway as a result of a polymorphism R72P are resistant to nutlin-3a apoptosis induction. The results suggest that MDM2 inhibition induced p53-dependent cell cycle arrest and apoptosis in wild-type TP53 glioblastoma cells. This effect seems to be at least partially because of Survivin down-regulation.

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

P.122. MANAGEMENT OF GlioblastOMA MultIFORME RECURRENCES

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Glioblastoma multiforme (GBM) is the most frequent form of brain tumor and the most malignant astroglial neoplasm. GBM comprises 15%–20% of all primary intracranial tumors and ~60% of astrocytic neoplasms. The incidence is in the range of 3–4 new cases per 100,000 population per year. It typically affects adults between 45 and 75 years of age, with a peak at 61.3. More than 80% of patients are older than 50. Despite progress in diagnostic procedures and treatment, prognosis in patients with GM is unfavorable and the survival time is limited. The crucial prognostic signs are the patient’s general and clinical condition of the patient. If not treated, the patient dies within several weeks after the diagnosis has been made. Surgery prolongs survival for ~8–10 months. Subsequent radiotherapy extends lifetime for an additional 3 months. Chemotherapy originally did not play an overly significant role.

Only the introduction of new alkylating chemotherapy Temodal for primary brain tumor brought a more significant change resulting in prolongation of both overall survival (OS) and performance-free survival (PFS). These problems with recurrent GM are evoked again. Our aims are to evaluate surgery indications, and also to achieve the planning of general treatment strategy. We would like to point our treatment strategy for recurrent GM out 15 patients group. Patients with tumors showing high PROX1 expression had been analyzed. The number of immunoreactive cells was used as a variable in multivariate survival analysis, together with established prognostic factors for this tumor. In a recent study, we have shown that PROX1 may act as a diagnostic marker for high-grade gliomas. The aim of this study was to address the prognostic value of PROX1 in a cohort of patients with grade II gliomas. A retrospective chart review of all adults with grade II gliomas operated between 1992 and 1999 at the Uppsala University Hospital, Sweden, was performed. Eligible paraffin-embedded tumor blocks were collected and a total of 128 samples were evaluated by immunohistochemistry for their PROX1 expression. The number of immunoreactive cells was used as a variable in multivariate survival analysis, together with established prognostic factors for this patient group. Patients with tumors showing high PROX1 expression had poor outcome, both in the univariate analysis (P = 0.0151) and multivariate analysis (P = 0.0250), compared with those with low PROX1 expression. When analyzing the separate histological subgroups, PROX1 expression was associated with shorter survival in astrocytomas and oligoastrocytomas but not in oligodendrogliomas. We conclude that PROX1 is a novel predictor of survival for grade II astrocytic gliomas.

P.124+. PROX1 IS A PREDICTOR OF SURVIVAL FOR ASTROCYTIC GLIOMAS BUT NOT FOR OLIGODENDROGLIOMAS GRADE II

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The clinical course of grade II gliomas remains variable and their transformation into a more malignant phenotype is highly unpredictable. There have been attempts to identify biological markers that can facilitate prediction of prognosis in individual cases of low-grade astrocytomas, but so far without much success. PROX1 is a transcription factor that plays a critical role in the development of various organs and has been ascribed both oncogenic and tumor suppressive functions in human cancers. In a recent study, we have shown that PROX1 may act as a diagnostic marker for high-grade astrocytic gliomas. The aim of this study was to address the prognostic value of PROX1 in a cohort of patients with grade II gliomas. A retrospective chart review of all adults with grade II gliomas operated between 1982 and 1999 at the Uppsala University Hospital, Sweden, was performed. Eligible paraffin-embedded tumor blocks were collected and a total of 128 samples were evaluated by immunohistochemistry for their PROX1 expression. The number of immunoreactive cells was used as a variable in multivariate survival analysis, together with established prognostic factors for this patient group. Patients with tumors showing high PROX1 expression had poor outcome, both in the univariate analysis (P = 0.0151) and multivariate analysis (P = 0.0250), compared with those with low PROX1 expression. When analyzing the separate histological subgroups, PROX1 expression was associated with shorter survival in astrocytomas and oligoastrocytomas but not in oligodendrogliomas. We conclude that PROX1 is a novel predictor of survival for grade II astrocytic gliomas.

P.125. PLEOMORPHIC GRANULAR CELL ASTROCYTOMA IN THE PINEAL GLAND

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

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

P.126. RADICAL SURGERY AFTER CHEMOTHERAPY FOR WHO GRADE II GLIOMAS: A STRATEGY PROTECTING NEUROCOGNITION AND QUALITY OF LIFE (ABOUT A SERIES OF 12 PATIENTS)
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OBJECTIVE: The aim of this study was to evaluate the impact on cognition and quality of life (QOL) as well as the results of a temozolomide (tmz)-based chemotherapy (CT) delivered before a radical surgery for WHO grade II glioma with Organization (WHO) grade II gliomas. PATIENTS AND METHODS: We selected patients treated by tmz and then by surgery for a WHO grade II glioma, from the database of two French centers (Montpellier and Nancy). Usual oncological data were collected. Patients benefited from the trial, at the end of the course, of a cognitive and QOL assessment. Global efficiency, laterality, executive functions, attention, information processing speed, psychomotor functioning, working memory, verbal and visual memory, language, visuo-spatial ability were considered for the cognitive assessment. Used tests will be presented. For the QOL, EORTC QLQ C30 + BN 20 scales were chosen. Radiological responses were evaluated by tumor volumes before and after CT and surgery. The presence of a gadolinium enhancement was systematically analyzed. RESULTS: Twelve patients with a median age at diagnosis of 40.5 years (22–51) and at assessment of 48 years (26–55.5) were selected. The median follow-up was 64 months (31.5–120) and the median time between assessment and the last surgery was 20.5 months (3–70). Symptoms at diagnosis were partial seizures (3/12), and cognitive difficulties were noticed in 10 patients (83%). Postoperative rehabilitation was offered to all patients. 11 patients benefited from a more or less complete resection (4/12), and 10 (83%) patients had a WHO grade II gliomas. CONCLUSIONS: The sequence “chemotherapy and then functional surgery” was proposed to help conceptualize the findings of the study and could be used to aid patients, families, and health professionals to reflect on, and better understand, parts of the early illness experience.

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

P.128. COMPARATIVE ANALYSIS OF IDH1 MUTATION, TP53 MUTATION, AND MGMT HYPERMETHYLATION IN ASTROCYTOMAS
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TP53: mutation, MGMT hypermethylation and, more recently, IDH1 mutations have been identified as precocious genetic aberrations in gliomas, but their mutual relationships during glioma formation have not been clarified. We performed a comparative genetic analysis in a selected group of 18 patients affected by low-grade astrocytomas and in these same patients at tumor recurrence, irrespective of anaplastic progression. The aim of the study was to investigate the natural history of disease, excluding the interference of the radio-chemotherapeutic agents. MATERIALS AND METHODS: We studied 18 patients affected by fibrillary astrocytoma (9), gemistocytic astrocytoma (3), protoplasmic astrocytoma (6). They did not undergo radiotherapy or chemotherapy after first surgery. After a median follow-up of 72 months, 15 of 18 patients occurred and the tumor showed a more malignant phenotype. Three patients underwent a third chirurgical intervention, all progressing to more malignant phenotypes. Specimens were investigated for MGMT hypermethylation using methylation-specific PCR after sodium bisulfite modification; LOH on chromosomes 1p, 9p, 10q, 17p, and 19q; IDH1 and TP53 mutations by sequencing analysis after PCR amplifications. RESULTS: Primary low-grade astrocytomas showed IDH1 mutation in 17 out of 18 cases, MGMT hypermethylation in 8 out of 18, and TP53 mutation in 8 out of 14. At recurrence, all MGMT hypermethylation and IDH1 and TP53 mutations in primary tumors were confirmed. Furthermore, all losses of heterozygosity observed in the first sample were present also at recurrence. While IDH1 mutations were already present in all primary tumors but one, the MGMT and TP53 status showed changes at recurrence: 3 primary MGMT unmethylated tumors becomes hypermethylated at recurrence and one of them, initially wild type for TP53, showed a TP53 mutation. A possible predisposing role of IDH1 toward accumulation of genetic aberrations was not investigated because of the small number of IDH1 wild-type patients at primary tumor. Finally, 5 patients out of 8 with MGMT hypermethylated and 8 of 10 with MGMT unmethylated at primary surgery acquired new losses of heterozygosity at recurrence. CONCLUSIONS: IDH1 mutation, MGMT hypermethylation, and TP53 mutations are precious events in astrocytomas. Our results confirm that IDH1 mutation is the earliest genetic aberration in these tumors and that is widely represented in low-grade astrocytomas. Interestingly, only tumors with unmethylated MGMT changed their methyl- ation status becoming methylated.
P.129*. FEASIBILITY AND TOLERABILITY OF INTRAVENTRICULAR THERAPY WITH ALTERNATING ETOPOSIDE AND LIPOSOMAL CYTARABINE: EXPERIENCE IN 33 CHILDREN WITH MALIGNANT BRAIN TUMORS
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Intrathecal chemotherapy is a crucial element in the treatment of leptome- ningeal disseminated brain tumors in children. We report on our experience with an intraventricular therapy with alternating etoposide and liposomal cytarabine concomitantly to conventional and/or antangiogenic chemother- apy. Since May 1998, patients received intrathecal etoposide at a dose of 0.25–0.5 mg x 5 days every 2–6 weeks for a total of 306 courses (1–41 per patient) via an Ommaya reservoir. Intrathecal methotrexate and mafos- famide were additionally administered to 10 and 2 children, respectively. From October 2004 on, liposomal cytarabine was added and 33 patients aged 8 months to 25 years with various intensely pretreated disseminated brain tumors received liposomal cytarabine (25–50 mg) via an Ommaya reservoir or sporadically by lumbar puncture (210 doses, 1–20 per patient). Dexamethasone was used concomitantly for 3–5 days to prevent arachnoiditis. To allow dose-intense treatment and potentially evade resistanc- e most patients received alternating courses of liposomal cytarabine and etoposide. Toxicities following liposomal cytarabine were headache (n = 10), nausea/vomiting (n = 8), ataxia (n = 1), meningo- mia (n = 2), and visual disturbance (n = 3), which were connected to benign cerebral hyper- tension in 4 children that improved after one time of pressure release by lumbar/intraventricular CSF removal. Etoposide was generally well toler- ated, although mild toxicities occurred (headache, n = 2; nausea/vomiting, n = 1). Since all patients received some sort of concurrent anti-cancer therapy, the efficacy of intrathecal therapy cannot be assessed independently.

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

P.130. OPTIC NERVE LOCALIZATION OF INTRACRANIAL GERM CELL TUMORS
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Intracranial germ cell tumors are usually localized along the midline (pinealear suprasellar) in Caucasians. Para axial tumors are mostly reported in Asian patients. Optic pathway germ cell tumors have been exceptionally reported. We report 3 of such cases in Caucasian patients. A 23-year-old male presented a diplopia with raised intracranial pressure, requiring ventriculo- peritoneal shunt. The MRI showed a localized pineal tumor associated with raised seric hCG (700 U/L). The treatment included chemotherapy (BEP) + 50 Gy focal radiotherapy. A progressive visual loss occurred 6 years later, with unilateral swelling of optic nerve. Pure germinoma was confirmed by biopsy. A 34-year-old male presented a diminution of vision predominately on the right side, a left lateral hemianopsia, and a bilateral atrophy of the optic nerves. The MRI showed a swelling of the right optic nerve, extending to the chiasm. Biopsy showed a pure germinoma, no dissemination was found on MRI and markers were negative. Strategy was according to GCT 96 SIOP protocol: chemotherapy (Etoposide ifosfamide and Carboplatin) followed by a 24-Gy radiation to the ventricular system and tumoral bed. Six years later, he relapsed in the bulbomedullar junction, out of the irradiation field. A 13-year-old boy presented headache, diabetes insipidus, a growth atrophy. MRI showed a pineal region tumor. CSF HCG was raised (90 UI/L). This “bifocal” secreting tumor was treated according to GCT 96 SIOP protocol: chemotherapy (Etoposide Ifosfamide and Cisplatin) followed by 54 Gy of protonbeam and pineal region. He relapsed 6 years later as a ventricular seeding with chiasmatic, right optic nerve bulb and pituitary localizations. AFP and HCG were elevated in CSF and serum, All 3 patients are currently in second remission and anti-angiogenic therapy followed by a 24-Gy craniospinal irradiation with respectively a 1-, 2-, and 3-year follow-up. These cases emphasize the need of careful evaluation of optic pathway in patients with CNS germ cell tumors, both at time of diagnosis and relapse. Visual symptoms may be misleading when patients present with raised intra cranial pressure. Isolated involvement of optic pathway at diagnosis is a rare disease and requires a biopsy. Decreased vision after radiation therapy is not always because of radiation.

P.131. RESULTS OF TREATMENT PEDIATRIC RECURRENT HIGH GRADE GliOM (HGG) WITH COMBINATION OF BEVACIZUMAB AND IRINOTECAN
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Recurrent HGG in children has a dismal prognosis with minimal improvements in survival seen following currently available salvage therapy. This study was conducted to determine if the combination of a novel antangiogenic therapy, bevacizumab, and a cytotoxic agent, irinotecan, is safe and effective for pediatric patients with recurrent HGG. From February 2008 till December 2009, 22 patients with progressive HGG were enrolled in this study (11 girls and 11 boys). Age 12.5 years (range, 5–17 years). Previously all patients received resection of the tumor followed by RT with parallel temozolomide and monochemotherapy of temozolo- mide. Relapse was documented by CT/MRI/PET. Median of follow-up was 6 months (range 2–17 months). In 19 patients (86.3%), the glioblastoma (G) was histologically verified, and in 3 patients (13.7%) ana- plastic astrocytoma (AA) was verified. Karnovsky was 50–100 (with median 80). All patients received 6-week cycles of combined therapy: bevacizumab 8 mg/kg + Irinotecan 125 mg/m2 days 1, 8, 22, 29 and 6 cycles of combined therapy together with anticonvulsant, 340 mg/m2 days (1), 8, 22, 29 days. Median of follow-up was 6 months (range 1–18 months). Median of number of cycles for a patient was 3.8 (range 1–10). Objective response (complete and partial) observed in 10 patients (59.1%); 1 patient with CR died in remission in 1.5 month after finishing therapy from leukoencephalopathy. The 18-month PFS in patients with GB was 0.11 and OS was 0.28. Objective response observed in 15 patients (78.9%); PD in 4 patients (21.1%). Median of OS was 10 months, median of PFS was 5 months. In all, 3 patients (100%) with AA was PD. Median of OS was 10 months and median of PFS was 7 months. No central nervous system hemorrhages occurred, but 1 patient developed leukoence- phalopathy. Combination of bevacizumab and irinotecan is an effective regimen in relapsed pediatric GB with acceptable toxicity. PFS in this group is higher than in patients with AA, what statistically proved (P = .05).

P.132. OVERVIEW OF CHILDREN WITH ANAPLASTIC ASTROCYTOMA
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INTRODUCTION. Anaplastic astrocytoma (AA) is a rare tumor of CNS in children, which differs from the adult prognosis if surgical treatment performed.

MATERIALS AND METHODS: From 2000 to 2005 37 pts at the age from 5 months to 16 years (median 8 years) with the first time verified AA were observed. 4 patients received only resection, 8 pts - resection and radiotherapy (RT), 25 pts - complex treatment (combination of resection, RT and chemotherapy (CHT)). Total resection of a tumor performed in 15 pts, subtotal - in 7 pts, partial - in 12 pts, biopsy - in 3 pts. 33 pts received RT in a dose of 50–60 Gy (median 55 Gy). CHT was carried out under various schemes depending on age. The pts under 3 years old (n = 6) received CHT by the protocol “Baby” POG. Pts older than 3 years received after RT: Temozol 200 mg/m2 (n = 11), protocol HIT-91 (n = 5) or PCV (n = 3). RESULTS. The median of follow-up was 46 months (7–150 months). 5-years PFS and OS for all group of pts was 32 ± 9 and 50 ± 9
% respectively. Medians of PFS and OS -24 and 60 mths respectively. PFS in pts with total resection was 69 %, subtotal - 42 %, partial -10 %, biopsy -0 % (p <0.01). 5-year PFS was 56 % in pts with complex treatment, 10% in pts with surgical treatment and RT or surgery alone (p = 0.02). In pts under 5 years 3-year PFS - 80 %, older 5 years - 24 % (p = 0.002). The PFS in pts older 5 years who received different schemes of CHT was NS (not significant). CONCLUSIONS. The best indicators of PFS associated with complete resection of a tumor, age of pts older 5 years. The results permit to consider CHT as an effective and obligatory element of complex treatment of AA. The scheme of CHT depends on age of the patient.

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

MENINGIOMAS

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

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

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

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INTRODUCTION: Surgical resection of cranial base meningiomas continues to present an enormous surgical challenge because of the complexity of the approaches and mainly of the possibility of discharging sequelae. In the past 2 decades, stereotactic radiosurgery has been advocated as the definitive treatment in the management of these tumors, as a first-line treatment or after incomplete resections, changing the current management protocols in the treatment of these meningiomas. MATERIALS AND METHODS: A retrospective review of 615 patients treated for single cranial base meningioma at our Gamma Knife Unit during the period 1993–2009 was performed, particularly selecting 233 cases followed for more than 2 years. RESULTS: Two-thirds of the patients were females, with a global median age of 55 (25–84). The most frequent location was the cavernous sinus (57%), followed by clival and petroclival regions (16.3%). Forty-five patients (23%) were operated on, and 187 patients had received previous radiotherapy. The mean treated volume was 11 cm3 (0.6–85). The mean follow-up time was 50 months (24–163), with 60 and 7 patients followed during more than 5 and 10 years, respectively. Volumetric control was obtained in 97% of patients, with a reduced volume in 71.2%, and stabilization in 26%. Clinically, 91% of patients remained stable, with an improvement in 2.5%. CONCLUSIONS: Gamma-knife radiosurgery is a safe and efficient technique in the control of cranial base meningiomas, with an excellent preservation of neurological function. It has displaced conventional radiotherapeutic treatments and is becoming a definite alternative to aggressive and potentially disabling surgical resections.

P.136. SURGICAL TREATMENT OF CENTRAL NERVOUS SYSTEM HEMANGIOPERICYTOMAS

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INTRODUCTION: Hemangiopericytomas (HPC) are rare, highly vascularized tumors derived from pericapillary cells or Zimmerman’s pericytes, which tend to recur locally and metastasize extraneurally. Treatment includes complete surgical resection followed by radiotherapy to optimize local recurrence control. We present our experience in the treatment of patients with HPC. MATERIALS AND METHODS: Retrospective analysis of clinical data from patients with HPC treated at the Department of Neurosurgery between June 1995 and February 2010 was reviewed to establish lesion location, associated symptoms, radiological features, preoperative embolization, intraoperative findings, postoperative complications, extent of resection, recurrences, and need for adjuvant radiotherapy. RESULTS: A total of 14 patients with HPC were subjected to surgery during this period, of which 9 were females (64%) and 5 males (36%). Mean age of patients in this series was 44 years (range 21–75), and mean follow-up duration was 50 months (range 7–147). Lesions were supratentorial in 7 patients (50%), infratentorial in 2 (14%), falco-tentorial in 2 (14%), skull base in 2 (14%), and dorsal spine 1 (8%). Headache was the most frequent symptom in 8 cases (57%) followed by neurologic deficits in 7 (50%). Endovascular therapy was used in 5 patients (35%). Complete surgical resection was achieved in 11 patients (78%) and subtotal resection in 3 (22%). Eight patients received postoperative radiotherapy (57%). Recurrences were observed in 5 patients (35%), 4 at the primary site, and 1 at the craniospinal axis. Four of these patients were reoperated, and subsequently

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

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

P.139. TREATMENT OF RECURRENT MENINGIOMAS WITH IMATINIB MESYLATE: A SINGLE-INSTITUTION EXPERIENCE
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BACKGROUND: Some irresectable and symptomatic meningiomas recur after conventional radiation therapy or stereotactic radiosurgery and present a therapeutic challenge. Evidence-based data for medical therapy for patients with malignant or recurrent and irresectable meningiomas can be deemed as insufficient. Because of the prevalent expression of PDGF receptors in meningiomas, imatinib mesylate, a tyrosine kinase inhibitor of PDGFR-alpha, -beta, c-kit, abl, and arg (Gleevec-targets), has gained interest as a treatment of choice in this patient group. METHODS: We selected 18 patients with recurrent meningiomas, aged 30–74 years (median 53.5 years), treated at our institution from 1996 to 2008. Nine patients (4 males, 5 females, median age 54.0 years) with positive immunohistochemical staining of at least one of the mentioned targets were initiated with a daily oral dose of 400 mg imatinib mesylate as first-, second-, or third-line systemic therapy. MRI was performed every 3 months or at clinical suspicion of progression. The median time from diagnosis to start of imatinib treatment was 36 months. Immunohistochemical staining was performed on formalin-fixed and paraffin-embedded tumor tissue with antibodies against PDGFR-alpha, -beta, c-kit, arg, and abl. RESULTS: Imatinib mesylate at a dose of 400 mg/day was well tolerated. Out of 9 patients treated with imatinib, 7 had stable disease and 2 progressed at the first scan after 3 months. We did not observe any complete or partial responses, though prolonged disease stabilization with a progression-free survival rate of 66.6% at 6 months could be observed. Overall median progression-free survival in the imatinib-treated cohort was 16 months (range =3–31 months). Interestingly, imatinib treatment had a favorable impact on overall survival of meningioma patients (log-rank test, P = 0.34). CONCLUSION: Single-agent imatinib mesylate is a well-tolerated therapeutic option with a high rate of disease stabilizations in recurrent meningiomas. Imatinib treatment seems to correlate with survival in our patients despite heavy pretreatment with other therapeutic agents. Although these data clearly need verification in a larger, randomized clinical trial, our observation favors the use of imatinib mesylate in recurrent meningiomas, particularly in lack of other therapeutic options.

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

BACKGROUND: Filum terminale ependymomas form a specific variant of spinal cord tumors. Histologically, most are myxopapillary (WHO grade I), although grade II tumors also occur. Controversy exists about the role of surgical removal (total vs subtotal) and technique (“en bloc” vs piecemeal) and about adjuvant radiotherapy. METHODS: We performed a retrospective analysis of 22 cases treated from 1992 until 2008 (average follow-up 64 months). Possible prognostic factors (dimensions, metastasis, surgical aspects, and radiotherapy) were analyzed. RESULTS: In 3 patients, metastases were found at diagnosis. Surgery was complete in 18 (including 2 with metastasis resection, in 4 “en bloc,” the others piecemeal), partial in 4. Histology showed myxopapillary type in 16 (4 metastatized), grade II in 6 (1 metastatized). Adjuvant radiotherapy was performed after incomplete resection and/or metastasis. Delayed radiotherapy was given in 2 cases after local recurrence and was given in 2 on a metastasis. At last follow-up, 1 patient died of progressive disease and 1 died of unrelated cause (tumor free). Five patients had been treated for recurrences. Of the 20 patients alive, 17 were tumor free and 3 had stable disease. The most important prognostic factor was initial tumor presentation: all 9 patients with malignant subtype died of unrelated cause (tumor free). Five patients had been treated for recurrence. The prediction of clinical tumor progression in an even more drastic manner.

P13 SPINAL CORD TUMORS

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

BACKGROUND: Filum terminale ependymomas form a specific variant of spinal cord tumors. Histologically, most are myxopapillary (WHO grade I), although grade II tumors also occur. Controversy exists about the role of surgical removal (total vs subtotal) and technique (“en bloc” vs piecemeal) and about adjuvant radiotherapy. METHODS: We performed a retrospective analysis of 22 cases treated from 1992 until 2008 (average follow-up 64 months). Possible prognostic factors (dimensions, metastasis, surgical aspects, and radiotherapy) were analyzed. RESULTS: In 3 patients, metastases were found at diagnosis. Surgery was complete in 18 (including 2 with metastasis resection, in 4 “en bloc,” the others piecemeal), partial in 4. Histology showed myxopapillary type in 16 (4 metastatized), grade II in 6 (1 metastatized). Adjuvant radiotherapy was performed after incomplete resection and/or metastasis. Delayed radiotherapy was given in 2 cases after local recurrence and was given in 2 on a metastasis. At last follow-up, 1 patient died of progressive disease and 1 died of unrelated cause (tumor free). Five patients had been treated for recurrences. Of the 20 patients alive, 17 were tumor free and 3 had stable disease. The most important prognostic factor was initial tumor presentation: all 9 patients with malignant subtype died of unrelated cause (tumor free). Five patients had been treated for recurrence. The prediction of clinical tumor progression in an even more drastic manner.

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INTRODUCTION: Neurofibromas are characteristic tumors of Neurofibromatosis type 1 (NF1). They arise as discrete or more diffuse plexiform tumors, growing along cutaneous and subcutaneous nerves and spinal rootlets. Spinal neurofibromas are present in at least 50% of NF1 patients, and in most cases are asymptomatic. They are very different from sporadic or Neurofibromatosis type 2–associated schwannomas in their cell composition, location, and behavior. There are scarce case reports and two small series with limited information, about clinical presentation and management of NF1 patients with spinal cord compression from spinal neurofibromas. The aim of the study was to review our experience in the management of these tumors. MATERIALS AND METHODS: A retrospective review of clinical data has been performed in our series of 205 NF1 patients, followed up, and treated in a neurofibromatous referral center based in a neurosurgical unit. Pre- and postoperative neurological status has been evaluated following McCormick’s classification in patients with myelopathy secondary to spinal root neurofibromas. Demographic, clinical, anatomical, and surgical data were collected. RESULTS: The mean age at presentation ranged from 29 to 53 years. Clinical presentation was quadriparesis in 3, paraparesis in 1, and monoparesis in 2 cases. The anatomical level was cervical in 4 and thoraco-lumbar in 2. Tumor was growing from either anterior or posterior roots. Large intraspinal tumors were radically resected in every case, sparing rootlets with small tumor nodules, through laminectomies or osteoplastic laminotomies. Five surgical events were followed by an upgraded performance, with full recovery in 2 from 4 patients. One patient, suffering from a long-standing severe quadriparesis, still presented a severe deficit even if no cases the tumor recurred or progressed after surgery. No kypotic deformity was observed at follow-up. CONCLUSIONS: Spinal cord compression secondary to spinal root neurofibromas is a known but infrequently reported complication in NF1. The risk of becoming symptomatic does not decrease with age. The cervical area is where more neurofibromas appeared, but caudal spinal cord was also affected. Resection of spinal root neurofibromas producing symptomatic spinal cord compression is followed by excellent functional results, except in patients with long-lasting severe neurological deficit. Although asymptomatic spinal neurofibromas should not be treated, surgery should be considered and planned as soon as symptoms appear for the best functional results.

P.143. MALIGNANT SPINAL CORD COMPRESSION IN A PATIENT WITH Glioblastoma
A. Tinchon, S. Obersdorfer, V. Nussgruber, and W. Grisold; LBI Neurooncology, Vienna, Austria

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

P.144. SPINAL CORD AND BRAINSTEM HEMANGIOBLASTOMAS IN PATIENTS WITH VON HIPPEL-LINDAU DISEASE: MICROSURGICAL RESULTS IN A REFERRAL CENTER SERIES
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INTRODUCTION: Cauda equina paraganglioma (CEP) is a rare tumor. The first case was described in 1970 and since then less than 200 cases have been reported. The origin of CEP is uncertain as the existence of paraganglia cells in the central nervous system remains a point of debate. There is a male predominance, and low back pain is the main symptom in more than 90% of patients, with sciatica in 72%. MRI is the study of choice and treatment consists of total excision if feasible. Definitive diagnosis can only be made after immunohistochemical investigation. CEP is classified as Grade II WHO and the prognosis is excellent. Nonetheless, tumor recurrence rate is 15.4%. We report the microsurgical management results of spinal cord and brainstem hemangioblastomas in a VHL referral center. MATERIALS AND METHODS: We reviewed a series of 11 patients (mean age 40 ± 15.4 years, range 21–66 years) who underwent 13 operations to remove 17 intraspinal hemangioblastomas: 5 in brainstem, 3 in the bulbo-medullary junction, 4 cervical, 6 thoracic, and 1 lumbar hemangioblastomas. All surgical procedures were performed by the same neurosurgeon (JMDc) in a VHL referral center. The indication for surgery was established by the appearance of clinical symptoms or evident growth of hemangioblastoma. RESULTS: Sensory deficit was the most frequent symptom, present in 10 patients (76.9%), followed by motor deficit in 7 (53.8%). Complete resection was possible in all cases. In the pre- and postoperative functional assessment, according to McCormick’s scale, clinical improvement was obtained in 9 patients (69.2%) with global stability in 12 (84.6%), and clinical deterioration in 1 from I to II functional level.

P.141*. SPINAL CORD COMPRESSION FROM NEUROFIBROMAS IN NEUROFIBROMATOSIS TYPE 1 PATIENTS
J. M. De Campos1,2, M. E. Kusak3, J. F. Fabregat1, D. T. Aguirre1, J. Ayerbe1, and J. L. Sarasa5,6; 1Neurosurgery, Fundación Jiménez Díaz, Madrid, Spain; 2Univ...
BRAIN AND LEPTOMENINGEAL METASTASES

P.1445. ROUTE OF INTRACEREBROSPINAL FLUID LIPOSOMAL CYTARABINE ADMINISTRATION, SAFETY, AND EFFICACY OF THERAPY IN NEOPLASTIC MENINGITIS

J. Pardo, C. Ruiz-Ocaña, L. González-Cortijo, and C. Álvez-Usoín; Hospital Universitario Quirón Madrid, Pozuelo de Alarcón, Spain

BACKGROUND: Recently, it has been reported by Glanz et al. that there was no difference between route of intracerebrospinal fluid chemotherapy administration, intraventricular vs intralumbar, with different drugs (eg, methotrexate or liposomal cytarabine) in terms of progression-free survival or overall survival. We present our experience in one single-center with liposomal cytarabine administered to patients with neoplastic meningitis. METHODS: We reviewed 22 patients with cytologically documented neoplastic meningitis because of solid tumor or haematological malignancies. All of them were treated with liposomal cytarabine. We examined the type of tumor (solid or haematological), overall survival (time from diagnosis till death or study cutoff), evolution of disease, and adverse events. RESULTS: Twenty-two patients were treated since December 2006 to March 2010. Seven of them received liposomal cytarabine by intraventricular administration; 15 by intralumbar infusion. Five had solid tumors and the rest haematological malignancies. Grade I–II overall survival was 9.04 months (6.01 for the CNS group and 9.86 for the lumbar group). In the intraventricular group, only 1 patient had serious adverse event (ventriculitis). In the intralumbar group, 2 patients developed chemical cauda equine syndrome; 1 developed optic papillitis; and 1 developed both headache and adverse events. CONCLUSIONS: Site of intra-CSF liposomal cytarabine is clinically relevant with fewer adverse events by intraventricular route.

P.1485. THE ROLE OF TEMOZOLOMIDE FOR PATIENTS WITH METASTATIC BRAIN DISEASE

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BACKGROUND: Standards of chemo- and chemo-radiotherapy for treatment of brain metastases is not available till present time. Purpose of this trial is to assess the efficacy of temozolomide (TMZ) as monotherapy, TMZ combined with whole brain irradiation (WBI), or combined chemotherapy of TMZ and irinotecan (I) and TMZ and cisplatin (DDP) in patients with brain metastases (BM) from non-small cell lung cancer (NSCLC), breast cancer (BC), or melanoma. METHODS: Ninety-seven patients were included in this study. Patients with BM from NSCLC (21 patients), melanoma (17 patients), and BC (17 patients) were treated with WBI (3 Gy/30 Gy) and concomitant TMZ therapy (75 mg/m²/day orally on Days 1–14). Patients with BM from NSCLC (7 patients), melanoma (17 patients) were treated with TMZ (150 mg/m²/day orally on days 1–5, every 4 weeks) as monotherapy. Eleven heavily pre-treated NSCLC patients (after I–II lines of chemotherapy and/or WBI) were treated with combined chemotherapy of I (250 mg/m²/day 6 intravenous, every 4 weeks) and TMZ (150 mg/m²/day orally on days 1–5, every 4 weeks). RESULTS: Observations of the
study were as follows: in the TMZ + WBI-treated patients with BM from NSCLC, 3 (14.3%) complete response (CR), 8 (38.1%) partial response (PR), 8 (38.1%) stabilization of disease (SD). The median overall survival (mOS) was 7.5 months. In the TMZ + WBI patients with BM from melanoma, 3 (17.6%) PR, 5 (29.2%) SD. The mOS was 6.6 months. Among patients with BC brain metastases, 2 (11.8%) CR, 11 (64.7%) PR, 3 (17.6%) SD. The mOS was 11 months. In the TMZ monotherapy patients with BM from NSCLC, there were 4 SD, 3 patients progressed. The mOS was 8 months. In the TMZ as monotherapy patients with BM from melanoma, 1 (5.9%) CR, 4 (23.5%) PR, and 7 (41.2%) SD. The mOS was 6 months. In the TMZ + 1 patients with NSCLC brain metastases, 7 (63.6%) SD and 1 patient progressed. In the TMZ + DDP patients with melanoma brain metastases, 2 PR, 4 SD, 1 patient progressed. The mOS was 8 months. CONCLUSIONS: TMZ with WBI showed high efficacy in patients with BM from NSCLC, BC, and melanoma. TMZ as monotherapy showed efficacy and good tolerability in patients with BM from melanoma and SD in patients with BM from NSCLC. Combined chemotherapy of TMZ and I in heavily pre-treated patients with NSCLC BM showed prolonged SD and good tolerability. The TMZ + DDP combination has pronounced high anticancer activity in patients with brain metastases from melanoma.

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

OBJECTIVE: To evaluate the efficacy and clinical and radiological follow-up (r-FU) of patients with brain metastases (BM) treated with radiosurgery at a single institute. MATERIAL AND METHODS: Between 2003 and July 2008, 150 patients with BM (61.6% solitary, 61.9% lung) were treated with either SRS or SRT; the majority underwent radiosurgery at a single institute. The follow-up period ranged from 3 to 60 months. The median follow-up period was 46 months. Patients were followed using a prospective radiological schedule at a 3-monthly interval. Patients lost to FU because of death (within 3 months) were assumed to have local failure. Endpoints were local control (LC), defined as no enlargement of the metastasis on MRI or CT scan, overall survival (OS), and progression-free survival (PFS). RESULTS: Parameters evaluated and comparisons between SRS and SRT treatments were made. All data were analyzed using univariate survival analyses. A total of 260 BM were irradiated; for 66% r-FU was available (23% had no r-FU because of early death). The median OS, PFS, and LC was 7 months (range 3 days–46 months), 4.0, and 6.0 months, respectively. There was a significant difference in OS between RPA classes (P < .001). Median PFS was 5.0 and 3.0 months for SRS and SRT treatment, respectively (P = .001). The 6 and 12 months, the LC rate was 46% and 37%. The sum of all target volumes irradiated per patient (PTV) was a significant prognostic factor for PFS (HR = 1.12/5 c increase in PTV; 95% CI 1.01–1.23), PTV was a significant prognostic factor for LC (HR = 1.15; c increase in PTV; 95% CI 1.04–1.27). The maximum dose corrected for fractionation dose (EQD2, α/β = 10) was a significant factor for LC (HR = 0.98/Gy; 95% CI 0.97–0.99). Toxicity (acute or late) grade ≥ 3 was observed in 15 patients, there was no significant difference between patients treated with SRS or SRT. Full 3D radiological evaluation of LC is ongoing and the results will be presented. CONCLUSIONS: There is a clear correlation between the total irradiated target volume on PFS and local control: with increasing metastasis volume, a decrease of local control and PFS is obtained. The shorter PFS for patients treated by SRT also reflects this volume effect as SRT is applied for patients with larger metastases.

P.150. MULTIDISCIPLINARY TREATMENT OF LEPTOMENINGEAL METASTASIS IN PATIENTS WITH LUNG ADENOCARCINOMA

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

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

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BACKGROUND: Methotrexate (MTX) is an important chemotherapeutic agent in the management of oncological and autoimmune diseases. It can be given intravenously or intrathecally and is frequently given in combination with other drugs. Methotrexate has been implicated in a variety of neurological complications. The acute or subacute neurotoxicity occurs within days to weeks after MTX therapy and is characterized by acute onset of focal neurological symptoms and mimics cerebrovascular stroke. While this syndrome has been described in several case report series in children, it is much less frequently seen in adults. OBJECTIVES: To describe the clinical course of a patient with subacute toxicity after intrathecal MTX and the corresponding abnormalities on imaging. METHODS: Case presentation and literature review. RESULTS: We report the case of a 29-year-old woman with acute systemic T-cell leukemia receiving systemic low-dose MTX, cytarabine, cyclophosphamide, doxorubicin, vincristine, and Peg-Asparaginase, as well as intrathecal methotrexate. Eighteen days after intravenous chemotherapy and 8 days after her seventh intrathecal MTX application, she presented with acute onset severe aphasia and difficulty mild right face and arm weakness. Cerebrospinal fluid was unremarkable. Magnet resonance imaging (MRI) of the brain revealed confluent restricted diffusion in the left greater than the right centrum semiovale and focally within the splenium of the corpus callosum. These lesion had no significant mass effect, no associated enhancement and were only minimally hyperintense on T2 sequence. The patient’s neurological symptoms resolved completely over the next 24 hours without specific treatment. Repeat MRI 6 days later showed resolution of the diffusion abnormalities. DISCUSSION: Our case is unusual given the age of the patient. Most reports in the literature of subacute MTX toxicity describe children. Whether children are more likely to suffer MTX toxicity as a result of different susceptibility or children are simply more commonly treated with intrathecal or high-dose methotrexate requires more investigation. It is particularly important to be aware of this chemotherapeutic side effect in adults, as they are more likely to be misdiagnosed as presenting with an acute cerebrovascular ischemic or hemorrhagic event. The mechanisms of subacute MTX toxicity are poorly understood. Imaging abnormalities obtained in our case suggest a transient cytotoxic white matter edema as the underlying mechanism in subacute methotrexate toxicity.

P.152. VERIFICATION FOR HEMATOLOGICAL TOXICITY OF TEMOZOLOMIDE

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INTRODUCTION: Although 4 years has passed after temozolomide started to be sold on the open market, there are a few reports regarding the hematological toxicity of temozolomide in Japan. We have examined for our own experiments in 62 cases. METHODS AND RESULTS: Sixty-two cases of initial and
recurrent malignant glioma (25 males, 37 females, average age 58.1 years old) were included in the study. The observation period was from February 2004 to June 2008. Seven cases for administered group on consecutive days (temozolomide 150–200 mg/m²; oral administration once daily for 5 consecutive days). Thirty-eight cases for administered group on alternate days (temozolomide 150–200 mg/m²; oral administration once for 5 consecutive days and then cessation of the drug for 23 days, Including 18 cases of private import). Fifteen cases for patients in five days alternate regime after forty two consecutive days. The grade classification was conducted for hematological toxicity at Common Terminology Criteria for Adverse Events (CTCAE) as follows. For leucopenia, Grade 2 had 19 cases (30%), Grade 3 had 16 cases (26%), and Grade 4 had 2 cases (3%). For lymphopenia, Grade 2 had 18 cases (29%), Grade 3 had 21 cases (34%), and Grade 4 had 9 cases (15%). For decrease in platelets, Grade 2 had 9 cases (15%), Grade 3 had 3 cases (5%), and Grade 4 had 6 cases (10%). In addition, 21 of 22 cases for daily administration indicated lymphopenia with Grade 2 or more and the lowest value was appeared at around the time of the post daily dose for 42 consecutive days. It is indispensable for the preventive administration of ST drug combination. There are 2 death cases to be considered as being related to temozolomide. (ii) Male (84 years old) died with a combination of lymphopenic complication and cardiopulmonary by administered group on alternate days. (iii) 53; 47%) than in HC (599 of 2395; 25%) (P = .0082). DISCUSSION: The presence of well-defined onconeuronal antibodies in ovarian tumor patients is associated with diagnosed malignancy as well as with onconeuronal antibodies (ONAs). MATERIALS AND METHODS: The study included 177 NPS patients originating from Western Poland. In sera of all subjects, indirect fluorescence (EUROIMMUN, Germany) was performed as a screening and Western blotting (EUROIMMUN) as a confirmation test for the presence of ONA. The diagnosis of NPS was based on Graus’ criteria. Five years after sensitization of onconeuronal antibodies, the follow-up was performed in 57 patients after obtaining informed consent. Data for follow-up originated from medical records, personal (out-patients clinic) or telephone contact. RESULTS: A 5-year follow-up was performed in 57 patients, and malignancy was found in 11 cases. In 8 patients, primary tumor was diagnosed before or at the time of onset of PNS symptoms. The most common was lung cancer (32%), breast cancer (16%), ovarian cancer (16%), Hodgkin lymphoma (10.5%), and prostate cancer (10.5%). In the studied group, 16 patients had anti-Hu antibodies, 14 had anti-Ri, 14 had anti-Yo, 7 were unidentified, and 6 were seronegative. During the follow-up period, 8 patients died, 4 with diagnosed neoplasia, 6 had well-defined onconeuronal antibodies (3 with anti-Hu and 3 with anti-Ri). The number of patients with well-defined onconeuronal antibodies who survived 5-year period was higher (n = 38; P < .0001), than those without well-defined antibodies (n = 11). Also more patients (P = .0192) without diagnosed malignancy (n = 34) survived when compared with cancer patients (n = 15). CONCLUSION: The presence of well-defined onconeuronal antibodies in NPS patients is associated with better prognosis. Among well-defined onconeuronal antibodies, anti-Yo are predisposing to 3-year survival in Western Poland population.

PARANEOPLASTIC NEUROLOGICAL SYNDROMES

P.153. HLA-DQ2+ INDIVIDUALS ARE SUSCEPTIBLE TO Hu ANTIBODY ASSOCIATED PARANEOPLASTIC NEUROLOGICAL SYNDROMES M. T. de Graaf1, J. W. K. de Beukelaar2, G. W. Haasom2, W. H. B. N. Verheij1, E. H. M. Vermorken1, A. Didelot1, J. W. Gratsma1, and P. A. E. Sillevis Smitt1.1Department of Neurochemistry and Neuropathology, Poznan, Poland; 2Department of Gynecological Surgery in Poznan. RESULTS: Classical NPS were diagnosed more frequently (P = .0192) without diagnosed malignancy (n = 34) survived when compared with cancer patients (n = 15).

P.154. A FIVE-YEAR FOLLOW-UP OF NEUROLOGICAL PARANEOPLASTIC SYNDROME PATIENTS IN WESTERN POLAND POPULATION S. Michalak1, A. Potak2, J. Rybakova1, and W. Kozubski3; 1Department of Neurochemistry and Neuropathology, Poznan, Poland; 2Department of Neurology, Poznan, Poland; 3Poznan University of Medical Sciences, Poznan, Poland; 4Department of Neurology, Poznan, Poland. INTRODUCTION: Neurological paraneoplastic syndromes (PNSs) are considered as rare, immune-mediated remote effects of systemic malignancy on nervous system. Long-term observations are not commonly performed and until now—in Polish population. The aim of this study was to evaluate the survival of PNS patients and its association with diagnosed malignancy as well as with onconeuronal antibodies (ONAs). MATERIALS AND METHODS: The study included 177 NPS patients originating from Western Poland. In sera of all subjects, indirect fluorescence (EUROIMMUN, Germany) was performed as a screening and Western blotting (EUROIMMUN) as a confirmation test for the presence of ONA. The diagnosis of PNS was based on Graus’ criteria. Five years after sensitization of onconeuronal antibodies, the follow-up was performed in 57 patients after obtaining informed consent. Data for follow-up originated from medical records, personal (out-patients clinic) or telephone contact. RESULTS: A 5-year follow-up was performed in 57 patients, and malignancy was found in 11 cases. In 8 patients, primary tumor was diagnosed before or at the time of onset of PNS symptoms. The most common was lung cancer (32%), breast cancer (16%), ovarian cancer (16%), Hodgkin lymphoma (10.5%), and prostate cancer (10.5%). In the studied group, 16 patients had anti-Hu antibodies, 14 had anti-Ri, 14 had anti-Yo, 7 were unidentified, and 6 were seronegative. During the follow-up period, 8 patients died, 4 with diagnosed neoplasia, 6 had well-defined onconeuronal antibodies (3 with anti-Hu and 3 with anti-Ri). The number of patients with well-defined onconeuronal antibodies who survived 5-year period was higher (n = 38; P < .0001), than those without well-defined antibodies (n = 11). Also more patients (P = .0192) without diagnosed malignancy (n = 34) survived when compared with cancer patients (n = 15). CONCLUSION: The presence of well-defined onconeuronal antibodies in NPS patients is associated with better prognosis. Among well-defined onconeuronal antibodies, anti-Yo are predisposing to 3-year survival in Western Poland population.

P.155. NEUROLOGICAL PARANEOPLASTIC SYNDROMES AMONG WOMEN IN WESTERN POLAND: A STUDY FOCUSED ON OVARIAN TUMORS S. Michalak1, A. Kosuta2, D. Szurek1, J. Krygowski1, S. Sajdak1, and W. Kozubski1; 1Department of Neurochemistry and Neuropathology, Poznan, Poland; 2Department of Neurology, Poznan, Poland; 3Department of Gynecological Surgery, Poznan, Poland. INTRODUCTION: The spectrum of primary malignancies in neurological paraneoplastic syndromes (NPS) patients differs among males and females. In females, gynecologic and breast cancers are most frequently diagnosed. The aim of this study was to evaluate underlying cancer in female patients with suspicion of NPS and neurological deficits or onconeuronal antibodies in ovarian tumor patients. MATERIALS AND METHODS: We included in the study 201 women from 395 patients with suspicion of NPS hospitalized in Department of Neurology in Poznan (Poland) in a time period 2002–2006. Based on Graus criteria, NPS were diagnosed in 113 females. In sera of all subjects, indirect fluorescence (EUROIMMUN, Germany) was performed as a screening and Western blotting (EUROIMMUN) as a confirmation test for the presence of onconeuronal antibodies. Eighty-five patients with ovarian tumors originated from subjects hospitalized between 2007 and 2009 in the Department of Gynecological Surgery in Poznan. RESULTS: Classical NPS were diagnosed more frequently (P < .000001) in patients with ovarian tumors (17%) than in subjects without clinical manifestation of malignancy (6%). However, in patients with other malignancies, it was higher (30%; P = .0072). Odds ratio for the presence of classical NPS in ovarian tumor patients was higher than in cases without malignancy (3.16; CI 1.10–9.03; P = .0233). In females with nonovarian carcinomas, odds ratio of classical NPS was higher (6.65; 1.87–23.63, P = .0323). In females with nonovarian carcinomas, odds ratio of classical NPS was higher (6.65; 1.87–23.63, P = .0323)
anti-NMDA antibodies in teratoma patients without neurological deficit. CONCLUSIONS: Classical NPS were found both in patients with neurological deficits preceding clinical diagnosis of malignancy and in cases with other brain tumors using NPS. Anti-NMDA antibodies can appear in ovarian teratoma patients without neurological deficit. Anti-CV2 antibodies were not found in ovarian tumors patients.

**Supportive and Palliative Care**

P.156. **Classification of Headache in Patients with Malignant Gliomas According to the International Headache Society (IHS) Criteria**
K. Woznica, V. Nussgruber, W. Grisold, and S. Oberndorfer; LBI Neurooncology, Vienna, Austria

**Background:** Approximately 50% of patients with malignant brain tumors suffer from headache. However, well-designed clinical studies concerning this frequent and heterogeneous neurological symptom are rare. The aim of the study was to investigate the frequency and clinical features of headache in the course of disease of patients with malignant gliomas. **Methods:** We included 36 consecutive patients with supratentorial malignant gliomas in a prospective consecutive study. All patients were recruited from a Neurooncology outpatient unit. Using a standardized protocol, information concerning different aspects of brain tumor headache and general descriptive data were obtained. Patients were investigated at the time of diagnosis of the brain tumor, during concomitant radiochemotherapy, and at time of tumor progression. **Results:** At diagnosis, 47% of all patients reported headache. Among these, according to the IHS criteria, tension-type headache was as frequent as migraine-like headache (each 41%). Headache as the first symptom of the brain tumor was present in 39% of patients. During the concomitant treatment period, 56% of all patients reported headache. The proportion of tension-type headache increased to 70%, whereas migraine-like headache decreased to 15%. At the time of tumor progression, all patients reported tension-type headache as the diagnostic criteria for “headache attributed to increased intracranial pressure or hydrocephalus caused by neoplasm” (IHS 7.4.1) were not fulfilled at any time. At diagnosis, 76% of the patients met the IHS criteria 7.4.2 for “headache attributed directly to neoplasm.” Only 10% of patients fulfilled these IHS criteria at the time of concomitant treatment, and no patient during tumor progression. **Conclusions:** This investigation reveals that according to the clinical diagnostic criteria (IHS: 7.4.1), “headache attributed to elevated intracranial pressure”, and also “headache attributed directly to neoplasm” (IHS: 7.4.2), can rarely be a diagnosed in patients with malignant gliomas. We recommend a modification of the diagnostic criteria of the IHS classification system for headache in patients with malignant gliomas.

P.158. **Intractable Headache Because of Neoplastic Meningitis in Two Patients with Glioblastoma**
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**Introduction:** Neoplastic meningitis in patients with malignant gliomas is rare complication in the advanced stage of the disease. Diagnosis of neoplastic meningitis can often be time consuming and misleading. From the clinical point of view, patients suffer from rapid neurological deterioration and intractable headache. In accordance with neurological signs and symptoms, the diagnosis can be established with MRI of the total neuraxis. **Case Studies:** One 37-year-old male and a 50-year-old female patient with glioblastoma received standard surgery and adjuvant radiochemotherapy. First patient developed headache 5 months after end of adjuvant treatment and second patient during concomitant treatment. Both patients experienced severe headache, not responding to steroids or conventional analgesics. High dosages of opiates showed only little clinical efficacy. The diagnosis of neoplastic meningitis was established by means of MRI of the neuraxis, showing typical enhancement of the meninges and contrast-enhancing bulky lesions together with neurological signs and symptoms. Because of rapid clinical decline, only supportive management was applied in both patients. Patients died shortly after the diagnosis of neoplastic meningitis. **Conclusions:** Neoplastic meningitis represents a fatal complication and control of its signs and symptoms are challenging. Malignant glioma patients with rapidly progressing intractable headache without showing clinical and radiological signs of increased intracranial pressure are highly suspicious for neoplastic meningitis. Only high-dose opiates may show some clinical benefit.

**Primary Central Nervous System Lymphoma (PCNSL)**

P.159. **Lymphomatosis Cerebri (LC) Presenting with Orthostatic Hypotension, Anorexia, and Paraparesis**
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**Introduction:** Primary central nervous system lymphoma (PCNSL) usually appears to be enhancing mass lesions on neuroimaging. In rare instances, PCNSL occurs as a diffuse infiltrative variant without mass lesion or blood–brain barrier compromise termed LC. In all published cases, LC presented as a rapidly progressive dementia. **Results:** A 58-year-old woman presented with subacute onset paraparesis, orthostatic hypotension, and 80-pound weight loss. Her symptoms progressed over 6 months and she developed headache. Brain MRI revealed venous sinus thrombosis and nonenhancing foci of FLAIR hyperintensity in periventricular white matter (WM), subcortical WM, and pons. MRI spine revealed enhancement of lumbar nerve roots. Cerebrospinal fluid suggested malignancy. Cytology was negative despite multiple samples. Bone marrow biopsy, body CT, and body PET were unremarkable. She had subtle radiologic response, but no clinical improvement following steroids. Two months later, she developed encephalopathy, quadraparesis, and progression of the WM lesions. She developed fluctuating hypotension and expired. Systemic autopsy was unremarkable. Gross appearance of the brain and spinal cord was normal, without discrete mass. Microscopic inspection revealed diffuse infiltration of the brain by large B-cell lymphoma. **Discussion:** Instead of dementia as in all prior published cases, this patient with LC presented with anorexia and orthostatic hypotension, a symptom usually associated with systemic disease. Dienecephalic infiltration is a neurologic cause of anorexia. Entities such as lymphoma, leukemia, or histiocytosis should be considered in patients with weight loss and WM lesions. Rarely, orthostatic hypotension has a CNS cause. Recognition that the brainstem WM lesions...
were tumor infiltration rather than chronic vascular disease may have prompted earlier diagnosis. LC has a variable presentation. A high index of suspicion is necessary to make the diagnosis. Early recognition is important since treatment can lead to prolonged survival or cure.

P.160*. PROGNOSTIC VALUE OF SERUM SOLUBLE INTERLEUKIN-2 RECEPTOR IN PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA

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Soluble interleukin-2 receptor (sIL-2R) is well known as a disease marker of systemic malignant lymphomas. However, clinical significance of sIL-2R in primary central nervous system lymphoma (PCNSL) is still unclear. We investigated relationships between serum sIL-2R or other clinical values and the prognosis in patients with PCNSL. The patients were 14 men and 12 women, mean age 66.9 years, treated in our hospital from November 2002 to August 2009. Mean follow-up period was 16.8 months ranging from 1 to 86 months. For the statistical analysis, the patients were grouped by the age (cut off: 70 years), the serum level of sIL-2R (cut off: 550 IU/mL), and LDH (cut off: 220 U/mL) before the treatment, and the treatment with or without methotrexate-based chemotherapy. The serum level of sIL-2R was not affected by the age. Kaplan–Meier analysis exhibited the tendency of poor survival among the aged population (P = 0.103). Higher serum level of sIL-2R related to the poor survival (P = 0.015), whereas no significant impacts of serum LDH level and chemotherapy were observed on the prognosis. Multivariate analysis using Cox proportional hazard model showed the serum level of sIL-2R was significantly associated with the prognosis (P = 0.025). Our study suggests that the measurement of serum sIL-2R might be useful as a prognostic indicator for PCNSL patients.

NEW DEVELOPMENTS IN SURGERY

P.161. EXTENT OF RESECTION AND OVERALL SURVIVAL AFTER INTRAOPERATIVE IMAGE-GUIDED BRAIN TUMOR SURGERY

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OBJECTIVE: The use of intraoperative MRI (iMRI) has been reported to improve the extent of resection in glioma surgery, indirectly influencing survival. Yet, randomized or at least comparative studies to prove its value are lacking. With this analysis, we aim to assess the influence of iMRI guidance on the extent of resection and survival of patients with glioblastoma (GBM). METHODS: We analyzed data of all consecutive patients with GBM undergoing intended complete tumor resection in our department between October 2007 and September 2009. All patients had a preoperative KPS of 70 or greater. Surgeries were performed using conventional microsurgical techniques with or without iMRI guidance, employing a mobile 0.15 T device. An independent neuroradiologist, blinded for the surgical treatment modality, assessed MRI data to determine the extent of resection. It was classified as complete if no, and incomplete if any residual contrast enhancement was detected on early postoperative MRI obtained at 3 T. All patients received adjuvant treatment and were followed on a 3-monthly basis. RESULTS: Of the 101 patients meeting the inclusion criteria, 87 had a primary and 14 had a secondary GBM. Overall, the extent of resection was complete in 68.3% and incomplete in 31.7% of cases. Intraoperative MRI guidance was used in 28 patients. In 7 of these patients (25%), intraoperative imaging depicted residual enhancing tissue leading to further tumor resection. In the iMRI group, a complete resection was achieved in 25 patients (89.3%) compared with 43 (60.3%) in the conventional group (P < 0.01). Mean age was 55.8 years, which did not differ between the iMRI guided and conventional microsurgery group (54.9 vs 56.2 years, P = 0.8). Until March 1, 2010, 23 patients have died. Mean follow-up was 50.5 weeks. Kaplan–Meier estimates rendered a mean overall survival of 91.1 weeks. There was no statistically significant difference between patients with primary vs secondary GBMs (P = 0.5). Young age (P < 0.01) and complete resection (P < 0.05) were associated with a better outcome. CONCLUSION: Even in dedicated centers, intended radiologically complete tumor resections cannot always be achieved in GBM surgery. In terms of extent of resection, the use of iMRI improves the surgical success rate compared with conventional microneurosurgical techniques. These results need further confirmation by a randomized trial.

NEW DEVELOPMENTS IN RADIOTHERAPY

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

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

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

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BACKGROUND: Since 1972 craniospinal irradiation (CSI) at The Christie has been delivered supine with a parallel pair of cranial fields and matching posterior wedge pair fields to the spine. This is delivered conventionally to reduce the dose to the thyroid, heart, and gonads. We report the survival and late effects of all adult medulloblastoma patients treated between 1980 and 2007 with this technique. METHODS: Medical records of patients ≥16 years old treated for medulloblastoma were analyzed retrospectively. Patients received 35 Gy in 20 fractions to the primary tumor boost of 20 Gy in 10 fractions. Ten-to-twenty-gray boost was given to metastases. Kaplan–Meier method was used to calculate overall survival (OS), time to relapse and relapse-free survival (RFS). RESULTS: Forty-seven patients were identified (19 females, 28 males). Median age was 25 (range 16–56). Twenty-two patients had MRI staging, 2 had myelograms, and 4 were metastatic at diagnosis. Surgery was complete in 8 patients, subtotal in 36, and 3 had biopsy only. Median time from surgery to RT was 33 days (range 11–107). Forty patients received 30 Gy to CSI, 5 received 35 Gy, and 2 received <30 Gy. Three had concurrent vincristine only, 3
had concurrent vincristine and maintenance chemotherapy with CCNU and cisplatin. Median follow up is 12.2 years. Nineteen of 47 relapsed (6 outside the radiotherapy treatment fields). Longest interval to relapse was 10 years. Five of 19 patients who relapsed are alive and in remission. The 5-, 10-, and 20-year RFS are 61%, 52%, and 49%, and OS are 68%, 52%, and 43%, respectively. At last follow up 27 live independently, 11 are employed, 9 are married, and 5 (3 males, 2 females) have had children post treatment. All remaining patients had undergone assessments: The mean hormone replacement treatment (3 growth hormone, 1 thyroxine, and 1 hydrocortisone). One patient developed epilepsy, 5 hearing impairment, and 2 second malignancies (breast, prostate). None developed meningioma, thyroid malignancies, or secondary BC. All patients were noted. CONCLUSION: We report the longest follow up data in adult medulloblastoma treated with a supine conformal radiotherapy technique. Our series is one of the largest and demonstrates survival comparable with published literature. Supine CSI is well tolerated by patients and reduces the long-term sequela on the heart, thyroid, and gonads.

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


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INTRODUCTION: MGMT studies have demonstrated that a limited number of patients with glioblastoma benefit from Temozolomide. The remainder of the patients depend on radiotherapy at a maximum radiation dosage of 60 Gy, with no safe means of dose escalation. Boron neutron capture therapy (BNCT) is a binary treatment modality which represents a biologically targeted means of radiation dose escalation targeting both cyclotronic and noncycloidal cancer cells1 without precluding other therapies. METHODS: We report on a Cancer Research UK clinical pharmacokinetic study of Boronophenylalanine (BPA) in patients with high-grade glioma to optimize uptake parameters for clinical trials of BNCT. The goals of the study were: to investigate the pharmacokinetic profile of BPA in the new mannitol-based formulation; to evaluate the toxicity profile of BPA–mannitol; and to optimize the dose and uptake parameters for BPA–mannitol for use in future clinical trials of BNCT by integrating the tumor-harvesting data based on LAT-1 distribution and activity into the final pharmacokinetic model for clinical studies. The study investigates the route of infusion and, in each case, will assess the effect of administration of mannitol as a blood–brain barrier disrupter. Measurements were made by Inductively Coupled Plasma Mass Spectrometry (ICP-MS) of 10B concentration in blood, urine, extra-cellular fluid (via brain macrodissection), brain tissue around tumor and tumor tissue. Additional analysis was performed using Secondary Ion Mass Spectrometry (SIMS). RESULTS: Peak Boron (10B) levels in blood were in keeping with previously published data but were significantly enhanced by the addition of mannitol. Tumor concentrations were variable, reflecting the heterogeneity of glioblastoma. Peak concentrations were not achieved in some patients until as late as 6 hours after infusion, later than previously shown. This peak concentration correlated with concentrations in extracellular fluid. Administration via the intra-arterial route enhanced the tumor concentration, peaking 2 hours after blood BPA levels. CONCLUSIONS: Previous clinical studies into BNCT for glioblastoma have suggested that irradiation at I hr after the end of BPA infusion. Our study shows delayed peak boron levels in brain and ECP suggesting that the optimal window for delivery of the radiation dose may be approximately 4 hours after infusion. Escalation of tumor boron dose without additional dose to normal brain is possible and likely to further facilitate therapeutic response.

REFERENCES


P.165. A COMPARISON OF VOLUMETRIC MODULATED ARC THERAPY (RAPIDARC) AND CONVENTIONAL EXTERNAL BEAM RADIOTHERAPY IN TEMPORAL HIGH-GRADE GLIOMAS

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INTRODUCTION: Patients treated for high-grade gliomas in the temporal region with external beam radiotherapy are at risk of significant cognitive deficits, including short-term memory loss which has a significant impact on daily functioning and quality of life. This is thought to be related to dose received by the hippocampi. Objectives: A feasibility study was done using RapidArc (3) (Varian medical systems), a volumetric arc–based intensity-modulated radiotherapy technique (IMRT) to treat high-grade gliomas in the temporal region and to establish if there was a dosimetric advantage of RapidArc compared with conventional radiotherapy with particular reference to dose to the hippocampi. METHODS: Ten patients previously treated with conventional 3D conformal radiotherapy for high-grade gliomas in the temporal lobe region were replanned using Varian RapidArc. Target volumes, organs at risk (OAR), and dose constraints defined for conventional planning were unchanged, but in addition hippocampi, inner ear, and temporal lobes were outlined using MRI fusion. No additional dose constraint was added for hippocampi. Comparisons of doses to the PTV and organs at risk including hippocampi were then made. RESULTS: The conformity index was much improved with RapidArc (typically 1.5 with conventional and close to 1 with RapidArc). Conformality was further increased by the use of more than 1 arc. Maximum doses to nearby critical structures such as optic nerves and optic chiasm were reduced with the use of RapidArc. There was a reduction in the volume of normal brain receiving a high dose. As these gliomas were within the temporal lobe, the ipsilateral hippocampus was within the PTV, so dose could not be reduced. Dose to the contralateral hippocampus varied from patient to patient. In some the contralateral hippocampus, dose was larger because of the increased volume receiving low doses with RapidArc. CONCLUSION: RapidArc is effective at reducing dose to OAR near to the PTV, improving conformity and reducing the volume of normal brain receiving a high dose of radiation in patients with temporal lobe gliomas. The use of RapidArc to improve conformity does not lead to hippocampal damage. However, the increase in conformity is thought to be due to the hippocampi-thalamus being more than 1 cm apart.

MISCELLANEOUS

P.166. AWAKE SURGERY DURING RESECTION OF INSULAR GLIOMAS

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PURPOSE OF THE STUDY: Insular gliomas are by many still considered imperable, because of anatomical localization, vascular supply, and the potential devastating complications. We present our experience with the operative treatment of patients with insular gliomas in an “awake craniotomy” setting. PATIENTS AND METHODS: Nineteen consecutive patients with an insular tumor were operated awake during the period 2003–2009. Pre-operatively, an extensive neuropsychologic/linguistic workup was performed. All patients underwent MRI with neuronavigation and when possible fMRI. After cortical stimulation, the Sylvian fissure and periinsular sulci were opened. Tumor resection was performed under speech and motor surveillance. RESULTS: The patients’ average age was 41.4 ± 10.3 years. Pure insular lesions were seen in 2 patients, a medial temporal base-insular glioma in 1, insular fronto-occipital and orbitofrontal-insular-temporal polar in 6 and 10 patients, respectively. Presenting symptoms included epilepsy (95%), dysphasia (26%), and cognitive problems (26%). In 13 patients, the resection was near total (95–98%) and in 9 patients in the remaining 6 patients. Histology confirmed 16 low-grade and 3 high-grade gliomas. The average follow-up was 2.1 ± 1.5 years. Perioperatively 9 patients clinically deteriorated. However, all patients with a low-grade glioma recovered to preoperative status. Two patients with a high-grade glioma have died during follow-up. CONCLUSION: Insular glioma surgery, facilitated by (sub)cortical stimulation in an awake setting, is feasible to acquire maximal cytoreduction in a safe manner. A dedicated surgical team is required, next to neurosurgeon, anesthesiologist, and patient interaction.
Most reported radiation-induced osteosarcomas arise from the facial bone or paranasal sinus after radiotherapy for retinoblastoma and/or pituitary adenoma. We report 2 radiation-induced osteosarcoma cases occurring in the paranasal sinus after treatment for frontal glioma.

CASE 1: A 56-year-old female underwent surgical resection of a left frontal tumor 16 years earlier in October 1990. The histological diagnosis was a low-grade glioma. After surgery and radiotherapy, she was discharged. In September 1996, a CT scan showed an osteolytic lesion in the right frontal region. A CT-guided biopsy was performed, and a histological diagnosis of radiation-induced osteosarcoma was made. The patient subsequently died of rapid tumor re-growth.

CASE 2: A 38-year-old male underwent partial resection of a bifrontal tumor in May 1996. The histological diagnosis was anaplastic oligoastrocytoma. Radiotherapy of 56 Gy was administered. The patient was subsequently readmitted in March 2008 because of a marked deterioration in general health. As tumor recurrence was suspected in the left frontal lobe and a CT scan showed an osteolytic mass in the right frontal sinus, a secondary operation was performed and the histological diagnosis was radiation-induced osteosarcoma. Radiotherapy was re-administered, but the patient died of rapid tumor re-growth. Radiation-induced osteosarcoma appeared 16 years after radiotherapy in Case 1, and 12 years after radiotherapy in Case 2. Given that the prognosis of radiation-induced osteosarcoma is poorer than that of primary osteosarcoma, careful attention is needed in considering the long-term survival of patients with glioma.
multi-modality therapy facing most glioma patients, including issues of patient and carer education, psychological adaptation, symptom control, the ongoing appropriateness of the therapeutic strategy, detailed planning and management of new surgical procedures, and obtaining informed consent. Possible objectives include forging closer ties with the physics department to develop stereotactic IMRT, and supine craniosurgical therapy delivery.

### P.171. CRANIAL BASE PARANGIOLIASMAS: GAMMA-KNIFE RADIOSURGERY

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**INTRODUCTION:** Parangioliasmas are highly vascular neuroendocrine tumors, usually benign and well encapsulated. In their cranial base location, microsurgery is associated to high morbidity (50%–80%) especially in relation to low cranial nerve damage. Gamma-knife treatment is emerging as a definitive therapeutic option in the treatment of these lesions.

**MATERIALS AND METHODS:** We present a series of 57 patients bearing cranial base parangioliasmas treated with Gamma-knife radiosurgery from February 1995 to January 2010. Forty-seven patients with a follow-up exceeding 2 years are analyzed in detail. There were 15 males and 19 females with a mean age of 53.7 years (range 19.9–82.3). In 31 cases, there was a neuroimaging diagnosis exclusively, the other 16 had been operated on and had a pathologically confirmed diagnosis. In the surgical group, 3 patients had their lesions previously embolized, and 2 had a history of radiotherapy while in the nonsurgical group 5 had received endovascular treatment and 1 had a monopolar radiotherapy.

At the time of treatment, 6% of the operated patients were asymptomatic, and 81% and 94% had low cranial nerve and VIII cranial nerve deficits, respectively. In the nonsurgical group, 3% were asymptomatic, with low cranial nerve involvement in 74%, and 71% and 23% with VIII and VI, or VII cranial nerve deficits, respectively. The mean tumor volume was 14.2 cm³ (1.4–62.2 cm³), with a mean marginal dose of 13.6 Gy (12–15 Gy) and maximal doses between 20 and 55 Gy. RESULTS: Mean follow-up was 65.5 months (12–175). Volumetric control was obtained in 93.6% (reduction in 68.1% and stabilization in 25.5%). Tumors progressed in three cases (6.4%). The volumetric reduction ranged from 0.75 cm³ (5%) to 14.2 cm³ (62.2%) (mean 5.6 cm³, median 3.4 cm³). No clinical complications were observed. CONCLUSIONS: Gamma-knife radiosurgery is an effective, safe, and efficient therapeutic option in the treatment of these tumors, as a first line treatment or associated to surgery, endovascular treatment, and/or conventional fractionated radiotherapy.

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

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**INTRODUCTION:** NF2 is an autosomal-dominant genetic disease with an incidence of 1 in 30,000 births and a prevalence of 1 case in 150,000 inhabitants. It is characterized by the simultaneous or consecutive development of intracranial or spinal meningiomas or schwannomas. The presence of bilateral VIII cranial nerve schwannomas is a main feature, with high surgical risks of cranial nerve deficits. **OBJECTIVE:** Analysis of our results of Gamma Knife Radiosurgery in this group of patients. METHODS: Between January 2006 and October 2008, 70 treatments in 33 NF2 patients have been performed, 13 patients were treated in more than one occasion (1–4 treatments, mean 1.6). Seventy-eight percent of patients have a complete follow-up. Two-thirds were females. The mean age was 36.5 (12–79). Fourteen patients had been previously operated (mean surgical procedures: 1.8: range 1–4) and 22 had received previous radiotherapy. The mean number of treated lesions in one procedure was 3.9 (1–18), with a mean marginal dose of 12.7 Gy and a mean treated volume of 10.4 cm³. There was a known family history for only one-third of patients. RESULTS: The mean follow up time was 4 years (5–188 months), with 20% of patients followed for more than 5 years. The local volumetric control was obtained in 72.8% of cases with reduction in 31%. One hundred and forty-nine meningiomas and 62 schwannomas were treated. In 13 cases, the treated lesions grew (12 schwannomas and 3 meningiomas). In 39 cases, new tumors appeared during follow-up. From a clinical point of view, 28 patients remain stable, in 5 their symptoms improved and, in those where there was a clinical deterioration, hearing worsened in 11 cases. Three patients died as a result of progression of NF2. CONCLUSIONS: Gamma Knife radiosurgery is an effective option to surgery in the treatment of NF2 patients, because of the minimal peripheral irradiation of healthy tissues, especially in meningiomas of patients previously operated on or with contra-indications to surgery. Having the knowledge of the genetic condition of this disease, where the potential oncogenic effect of radiotherapy should be taken into account, any therapeutic decision must be evaluated individually. This treatment must be used in those patients with lesions with evident growth or with progressive symptoms, when surgery is not a safe option in an NF2 experienced neurosurgical unit.

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

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

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

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**INTRODUCTION:** Cognitive difficulties (CDs) are very common in patients with gliomas, and their origin is multifactorial: tumor, surgery, radiotherapy, chemotherapy, antiepileptic drugs, steroids, and anxiety and depression are commonly described factors. However, the prevalence of CD is difficult to estimate. Discrepancies among studies are frequently explained by methodological differences. Performance status scales (KPS, ECOG) and short screening tests for CD (MMSE, MDRS) have a low sensitivity to detect CD in patients with gliomas, particularly in those with mild impairment and/or pre-morbid function. A better approach is to use a battery of tests directed to evaluate the cognitive domains more frequently impaired in these patients. METHODS: Patients with primary brain tumors and CD were recruited from the Neuro-oncology Clinic. All subjects were evaluated with a selected battery of tests that examine the cognitive domains more frequently affected by cancer and its treatment (attention, memory, and executive function); similar batteries have shown usefulness to evaluate cognitive function in patients with gliomas. Tests are standardized for Spanish population. A screening test for anxiety and depression and a quality of life tool were also included. The battery comprises: Rey Complex Figure Test, Word list (WMS-III), Digit-Span Test, Symbol Digit Modalities Test, Trail Making Test A&B, FAS, STROOP, HADS, and EORTCQLQ-C30. RESULTS: A total of 7 patients were evaluated up to now. Median age was 43.5 years (28–68); 2 were men and 5 were women; all patients had at least primary studies. Tumor diagnosis was grade III glioma (2), grade II glioma (3), grade I glioma (1), and meningioma (1). Test results show more deficits in delayed performance compared to healthy controls.
recall, working memory, mental flexibility, and verbal fluency compared with normalized population, in the absence of anxiety or depression. Completion time test was ~1 hour. Recruitment of further patients and a control group matched by age, sex, and level of education is currently ongoing. CONCLUSIONS: The introduction of a battery of cognitive tests for cognitive and quality of life evaluation was feasible and well accepted by patients. This experience will serve as a basis for future development of cross-sectional and longitudinal studies of cognitive function and quality of life in patients with gliomas in our environment. There is a need for specialized neuropsychological assessment in neuro- oncology patients.

P.177. POTENTIATING EFFECTS OF PARP INHIBITION ON CHEMO- AND RADIOTHERAPY TREATMENT IN SERUM-FREE GLIOMA CULTURES

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INTRODUCTION: The dismal prognosis of patients diagnosed with glioblastoma multiforme (GBM) urges researchers to investigate new treatment modalities for targeted drug regimens. Recent reports on glioma tissue cultured under serum-free (SF) conditions show that glioma stem cells (GSC) are preferably selected, and that these cultures preserve a good resemblance to the original tumor on DNA and RNA level. Several publications have illustrated GSC’s to be more resistant to chemotherapeutic or radiation therapy. This led us to develop a high throughput model for screening promising combination therapies. By isolating GSC’s from freshly isolated high-grade glioma (HGG) samples, we were able to test the effect of poly(ADP-ribose) (PARP) inhibitor ABT-888 in combination with temozolomide (TMZ) and radiotherapy (RT). METHODS: Freshly isolated HGG cultures were cultured under SF conditions as neurospheres. SNP analysis of both low (p1-p4) and higher passages (p7-p11) illustrated the genetic stability and resemblance to the parental tumor tissue. The samples that were successfully expanded were tested in several cytotoxicity studies. Cells were seeded in monolayer on 96-well plates coated with extracellular matrix. Treatment consisted of TMZ (100 μM) or RT (3 and 6 Gy) alone, or in combination with ABT-888 (250 nM), or TMZ (100 μM), RT (3 and 6 Gy), and ABT-888 (250 nM) in combination. The combined effect with ABT-888 was tested with aforementioned dosing of TMZ or RT, combined with 2.5 or 10 μM of ABT-888. Read out of therapeutic effect was assessed on Day 5 and 8 by performing the CellTiter-Glo assay (Promega). RESULTS: From these pathophysiological studies of these lesions was reviewed. RESULTS: Only 44 cases (28 intracranial, 16 spinal) have been reported to date. The majority occur in adults over 40, with a slight male predominance. Neurological symptoms result from local mass effect; however, seizures are also frequently observed. Imaging demonstrates central calcification with variable contrast enhancement. Histopathologically, a variably calcified chondromyxoid matrix with surrounding gliosis and without mitoses or cellular atypia is characteristic, suggesting a reactive origin to the lesion. In all reported cases, surgical excision is curative with only one reported case of recurrence. No further treatment is required, although routine surveillance may be of benefit. CONCLUSION: Although uncommon, awareness of this entity and its inclusion in the differential diagnosis of long-standing calcified lesions along the craniospinal axis has practical importance in preventing unnecessarily aggressive investigation and treatment.

P.176. INVESTIGATION ON THE INCIDENCE, PREVALENCE AND MORTALITY RATE IN FIVE CITIES/DISTRICTS IN EASTERN AND NORTHERN CHINA

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PURPOSE: To provide accurate, population-based incidence rate, prevalence rate, and mortality rate of primary brain tumor in the Chinese population. METHODS: We investigated 5 big communities in China. They were Baoshan district of Shanghai city, Longnan district of Daqing city, Ma’anshan city, Shu-yin city, Pu-yang city. The incidence, prevalence, and mortality rates from October 1, 2003 to September 30, 2006 were measured. RESULTS: The incidence rate, prevalence rate, and mortality rate of primary brain tumors in the investigated areas were 10.5/100,000, 24.5/100,000, and 4.3/100,000 respectively. Among males, these rates were 8.3/100,000, 20.3/100,000, and 3.6/100,000 respectively, and for females, 12.8/100,000, 29.0/100,000, and 5.1/100,000. The incidence rate for glioma was 3.13/100,000. CONCLUSIONS: This is the first report on the incidence rate and prevalence rate of primary brain tumors in China. Further study on the different histological subtypes and the etiology and risk factors of brain tumors are warranted.

P.175. A LITERATURE REVIEW OF FIBRO-OSEOUS PSEUDOTUMOR: THE ROLE OF SURGICAL EXCISION

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BACKGROUND: Fibro-osseous lesions are a rare clinical entity. We present the case of a 65-year-old female with infrequent partial seizures. Electroencephalography revealed Grade I dysrhythmia of the right hemisphere and an MRI revealed a calcified lesion in the right precentral frontal lobe. The patient underwent surgical resection and histopathology revealed a fibro-osseous pseudotumor. No further treatment was required and the patient is symptom-free 1-year post-operatively. METHODS: A review of all existing cases of fibro-osseous lesions was undertaken. The clinical and radiographic characteristics, histopathology, management and outcome of each case were evaluated. The suspected pathophysiology of these lesions was reviewed. RESULTS: Only 44 cases (28 intracranial, 16 spinal) have been reported to date. The majority occur in adults over 40, with a slight male predominance. Neurological symptoms result from local mass effect; however, seizures are also frequently observed. Imaging demonstrates central calcification with variable contrast enhancement. Histopathologically, a variably calcified chondromyxoid matrix with surrounding gliosis and without mitoses or cellular atypia is characteristic, suggesting a reactive origin to the lesion. In all reported cases, surgical excision is curative with only one reported case of recurrence. No further treatment is required, although routine surveillance may be of benefit. CONCLUSION: Although uncommon, awareness of this entity and its inclusion in the differential diagnosis of long-standing calcified lesions along the craniospinal axis has practical importance in preventing unnecessarily aggressive investigation and treatment.

P.178. DEVELOPMENT OF A DRUG SCREENING ASSAY BASED ON PATIENT-DERIVED GLIOMA CELL CULTURES WITH GENOTYPIC RESEMBLANCE TO THE PARENTAL TUMOR

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INTRODUCTION: The culturing of cells that mimic the molecular and cellular aspects of gliomas is essential for the development of more reliable preclinical tumor models. We set up a protocol to efficiently grow low passage serum-free (SF) and serum-supplemented (SS) cell cultures from patient tumor material. We tested various coatings to allow growth of serum-free cultures in monolayers instead of neurospheres. The genotypic profiles of both SF and SS cell cultures were compared with the parental tumor. METHODS: Tumor tissue was enzymatically dissociated and split at equal concentration into either SF or SS conditions. SS cultured cells were split at 80–90% confluence. SF cultured cells were grown as neurospheres (NS). NS cultures were dissociated with trypsin and seeded as NS or as monolayer cultures on various extracellular matrix (ECM) coatings. Expansion was scored as successful when cultures reached up to 5 passages, with expansion sufficient for pellet harvesting and low passage drug screening assays from p4 onward. DNA was isolated from snap frozen tumor sample or cell
pellets. For 3 individual patient series, we analyzed for copy number aberrations (CNAs) on Affymetrix SNP 6.0 arrays. RESULTS: In 12 months, a total of 59 glioma samples were collected; of which, 31 (52%) were propagated successfully. The success rate of SS cultures were solely dependent on the tumor size whereas the success rate in SF cultures was dependent on both sample size and initial amount of NS formation. SF tumor neurosphere cultures could be successfully transferred to monolayers in 96-well plates by seeding the cells on growth factor-reduced ECM coating, thereby attaining a model for drug screening. Successfully propagated tumors had similar genetic aberrations as the primary tumor. Genetic aberrations include high copy amplification of Chr.7p11 (EGFR) and loss of Chr. 9p (CDKN2A) and Chr10, all of which are common genetic aberrations in gliomas. Some CNA became more apparent in SF cultures through selective clonal expansion. Importantly, SS cultures showed a gradual loss of CNAs in higher passages. CONCLUSIONS: We developed an efficient protocol for SS and SF culture derivation of surgically removed tissue. Using growth-factor-reduced ECM coating, we are able to culture monolayers of GBM cells under SF conditions, which allows high throughput screening of patient-derived tumor cells with genetic profiles resembling the parental tumor up to high passages. However, the lower success rate of obtaining viable SF cultures remains a disadvantage. Moreover, we have determined the genetic aberrations of SS cultured material to be similar to tumor tissue in low passages (up to p4). This is, for practical and financial reasons, an attractive option next to SF cultures.

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

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