Methods: The SRT program to treat pituitary adenomas was initiated in 1997. The clinical outcome of all patients treated with SRT up to 2007 were retrospectively reviewed (n = 83). Median age was 47 years (range: 14−73), with 46 males and 37 females. Twenty patients had functional and 63 had non-functional tumors. Median follow up was 42 months (range: 1−137). Two patients received SRT as their primary treatment, 38 received it postoperatively and 9 for raised hormones. Thirty-four patients received SRT for radiological progression despite prior surgery with median time to progression following surgery being 12 months (range 1−275). Before SRT, hormone replacement therapy was observed in 37% (thyroid), 35% (cortisol), and 30% (testosterone, males only). SRT dose was 50 Gy in 25 daily fractions using the GTC frame, and CT-MR fusion for planning (Radionics^{TM}). Arcs were used in 66 patients and stationary 4−6 non coplanar fields in 17. The GTV and sella contents were treated, with no expansion from CTV for PTV margin. The prescription guideline was > 95% coverage of the CTV by a minimum dose of 47.5 Gy, and maximum dose <52.5 Gy.
Results: The 3-year progression free survival rates for functional and non-functional adenomas were 94% and 92% respectively (p = 0.90). Four patients had progression (3 nonfunctional and 1 functional); among these, 2 had metastatic spread. One patient had salvage excision, 1 had radiosurgery, 1 patient required temozolamide for lepto-meningial disease and 1 required palliative radiation to treat lumbar bony metastases. Post SRT 43 patients (52%) had hypothyroidism, 35 (42%) required cortisol and 20 (24%) required testosterone. 1 patient had severe optic neuropathy. To date there were no second cancers.
Conclusion: Though with a relatively short follow up, this study suggests fractionated stereotactic radiotherapy with a narrow margin is safe and effective for the treatment of pituitary adenomas. The results compare favorably with historical outcomes achieved with conventional 2 or 3-field techniques.

8733 POSTER

Atypical meningioma: outcomes and prognostic factors

H.J. Park[1], I.H. Kim[1], H.W. Jung[2]. [1]*Seoul National University Hospital, Radiaton Oncology, Seoul, Korea;* [2]*Seoul National University Hospital, Neurosurgery, Seoul, Korea*

Background: To retrospectively analyze and assess the outcomes and prognostic factors in atypical meningioma.
Methods and Materials: From April 1990 through April 2008, 45 patients with histologically confirmed atypical meningioma(WHO Grade ll) were treated with surgery and/or radiotherapy as a primary therapy at our institution. Of 45 evaluable patients, 21 patients were treated with surgery alone and 24 patients received surgery plus postoperative EBRT. Fifteen out of 21 patients who had a gross total resection(GTR) and nine out of 16 patients who had other than GTR received adjuvant EBRT. The median postoperative radiation dose was 61.2 Gy (range, 54−61.2 Gy). The median age at presentation was 52 years (range, 13−75 years) and the male:female ratio was 18:27.
Results: The 10-year cause-specific survival rate was 96.6% and 3- and 5-year progression-free survival(PFS) rates were 73.7% and 56.7%, with a median follow-up of 37.4 months (range, 6.1−217.8 months). Only one patient died from local failure and no one had distant failure. The 5-year PFS rates of patients treated with GTR only, GTR plus EBRT, other resection only, and other resection plus EBRT were 46.4%, 77.9%, 0% and 55.6%, respectively. Better PFS was significantly influenced by initial postoperative EBRT ($p = 0.025$), GTR ($p = 0.002$), male ($p = 0.033$) and Ki-67 <5% ($p = 0.002$) on univariate analysis. By multivariate analysis, postoperative EBRT, GTR, and male were associated with better outcomes.
Conclusions: In patients with atypical meningioma, postoperative radiotherapy improved progression-free survival, regardless of the extent of surgical resection. Besides adjuvant radiotherapy, GTR, male, and low Ki-67 proliferative index were independent predictors of the successful local control.

8734 POSTER

Oncolytic virotherapy of malignant glioma in an animal model using parvovirus H-1 (H-1PV)

I. Kiprijanova[1], K. Geletneky[2], A. Ayache[2], B. Leuchs[1], J. Schlehofer[1], J. Rommelaere[1]. [1]*Deutsches Krebsforschungszentrum, Tumorvirology, Heidelberg, Germany;* [2]*University of Heidelberg, Neurosurgery, Heidelberg, Germany*

The current standard of care for malignant gliomas is surgical resection and radiotherapy followed by extended adjuvant treatment with the alkylating agent temozolomide. Regrettably, this standard treatment paradigm has only a modest effect on patient survival. Resistance to radiation and chemotherapy remains an obstacle to the treatment of brain tumours. We have demonstrated that rodent H-1 Parvovirus (H-1PV) wild type, replicating efficiently in glioma cells, may overcome the limitations of conventional therapies by its oncolytic activity. This hypothesis is supported by findings on the sensitivity to the killing effect of the virus. Normal (non-tumor) cells were found to be unsensitive to the oncolytic effect of H-1PV. In vivo, H-1PV was tested for its efficacy and safety in treatment of a rat glioma in an animal model. A single stereotactic intratumoural injection of wild-type H-1PV was sufficient for remission of intracranial gliomas (established from RG2 cells in Wistar rats) without any damage of normal brain tissue or other organs. Similarly, intravenous injection of H-1PV led to complete cure of the brain tumours with no side effects. Furthemore, tumors derived from human glioma cells in immunodeficient rats could also been shown to be sensitive to H-1PV. The contribution of immunological factors to the oncolytic activity of H-1PV is currently under investigation.
These results are the basis of a planned clinical trials on H-1PV virotherapy.

8735 POSTER

Selection of candidate genes involved in glioma pathogenesis using bioinformatics tools

C. Diez-Tascón[1], J.M. López-Martí[1], O.M. Rivero-Lezcano[2], G. Santín-Piedrafita[1], C. González-Cortés[2], T. Ribas-Ariño[1]. [1]*Hospital de León, Servicio de Anatomía Patológica, León, Spain;* [2]*Hospital de León, Unidad de Investigación, León, Spain*

Human malignant gliomas are the most frequent form of brain tumours. They are commonly resistant to chemotherapeutic and radiotherapeutic treatments and their diffuse or infiltrative nature prevents surgical cure. The discovery during the last decade of molecular and epigenetic alterations have proven prognostically useful, but few advances have been made in the understanding of the complex mechanisms of tumour pathogenesis.
The present work deals with the selection of candidate genes potentially involved in the origin or progression of astrocytoma, the most frequent diffuse glioma. Our working hypothesis is that low and high grade astrocytoma should show differences in the expression of genes involved in biological functions that participate in tumour pathogenesis. In order to identify those functions, we used the bioinformatics tool “Gene Set Enrichment Analysis (GSEA)” to compare the following microarray experiments available in public databases: GSE4290, GSE3185, GSE1993, GSE2223 (from GEO database) and E-MEXP-597 (from ArrayExpress database). Results were obtained in terms of Gene Ontology (GO) categories (Biological process, Metabolic process and Cellular Component). Next, we selected the GSEA high scoring genes (“core enrichment”) associated to high grade (54 genes) and low grade (55 genes) tumours, in at least four of the experiments. Results were verified by the comparison of both gene lists using Fatigo+, a functional profiling method. In general, differentially expressed functions (GO hierarchy level 3) were (a) Biological process: “Cellular metabolic process”, “Macromolecule metabolic process” and “Primary metabolic process”; (b) Molecular functions: “Ion transporter activity”, “Nucleic acid binding” and “Hidrolase activity”; (c) Cellular component: “Membrane bound organelle”. We observed that specific high grade tumours share common functions with low grade tumours. This is consistent with the hypothesis that secondary tumours are generated by the evolution of low grade tumours, while primary tumours arise de novo.
Results of differential expression experiments using low and high grade tumour samples for two of the identified genes are presented.

8736 POSTER

Correlation between immunoreactivity of monocarboxylate transporter 1 in malignant glioma and tumor response to continuous intrathecal infusion of sodium butyrate

H. Nakagawa[1], M. Yoshida[1], M. Shindo[1], H. Nishiyama[1], T. Motozaki[1], K. Yoshioka[2], K. Itoh[2]. [1]*Nozaki Tokushukai Hospital, Neurosurgery, Osaka, Japan;* [2]*Osaka Medical Center for Cancer & Cardiovascular Diseases, Biology, Osaka, Japan*

Background: It has been suggested that the monocarboxylate transporter 1 (MCT1), which is part of the monocarboxylate transporter family, plays a major role in the uptake of butyrate. MCT1 in glial limiting membranes may play a role in equilibrating monocarboxylates between the brain cortex and the cerebrospinal fluid (CSF). Moreover, MCT1 immunoreactivity was strongest in high-grade glial neoplasma. However, sodium butyrate (NaB) is expected to be clinically useful because of its biological effects on cellular proliferation, differentiation, apoptosis and invasive metastasis. Therefore, NaB administered via the CSF enters the brain by abundant MCT1 in the glial limiting membrane, and then is distributed in the brain, where NaB is associated with MCT1 in the tumor itself. Thus, abundant MCT1 expression not only by tumor cells but also by the glial limiting membrane and ependym is supposed to facilitate a positive treatment effect of continuous intrathecal administration (CIA) of NaB for malignant glioma (MG).

Methods: Sixty milimolar NaB was continuously administered intrathecally to 23 patients (pts) with recurrent or progressive MG using a balloon pump system and treatment was continued as long as possible by changing the pump containing NaB weekly. MCT1 expression was also examined by immunohistochemical staining with specific rabbit polyclonal anti-bodies in the center of the tumor and the brain tissue surrounding the tumor in specimens obtained just before commencement of CIA of NaB in 18 pts with recurrent or progressive MG, and the correlation of MCT1 expression with clinical response was evaluated.
Results: Sixteen of 20 evaluable pts showed anti-tumor effects including tumor regression in 11 pts. The overall median survival time of MG was 11.0 (330 days) months. Four of 5 pts with CSF tumor cell dissemination showed a therapeutic response, including temporary negative cytological conversion. However, specimens in all pts responded to the therapy showed marked MCT1 expression in the tumor. By contrast, 4 pts, who did not respond to therapy, showed a low grade of MCT1 expression in the tumor.
Conclusion: The present therapy was well tolerated, resulted in long-term inhibition of tumor growth in some pts, and showed therapeutic safety. The most important favorable factor influencing the response to CIA of NaB was high grade of MCT1 expression in the nucleus and cytoplasma in the center of the tumor.

8737 POSTER

High resolution analyses of loss of heterozigosity (LOH) of chromosome 22 by SNP-arrays and microsatellite markers in meningiomas

M.D. Tabernero[1], C. Diez-Tascón[2], A. Maíllo[3], A. Castrillo[3], P. Sousa[3], M. Merino[3], A. Orfao[4]. *[1]IECSCYL-Hospital Universitario-Centro de Investigación del Cáncer IBMCC/CSIC-USAL, Unidad de Investigacion, Salamanca, Spain; [2]Hospital Virgen Blanca de León, Servicio de Anatomía Patológica, León, Spain; [3]Hospital Universitario de Salamanca, Servicio de Neurocirugía, Salamanca, Spain; [4]Centro de Investigación del Cáncer IBMCC/CSIC-USAL- Universidad de Salamanca, Servicio General de Citometria Departamento de Medicina, Salamanca, Spain*

Background: The most frequent chromosomal losses in meningiomas affect the long arm of chromosome 22. Several molecular technologies have been applied to find candidate genes in this chromosome. Microsatellite markers PCR analysis has been used to determine loss of heterozigosity (LOH) and actually single nucleotide polymorphisms (SNPs) arrays are avalaible to search LOH regions, that is consider a key event in the origen of many cancers. Our objective were to perform a genome wide study of LOH of chromosome 22 in meningioma patients using SNP-arrays and results validate with microsatellite markers.
Material and Methods: In the present study, chromosomal 22 LOH regions were analyzed by SNP-arrays in 50 meningioma paired samples with a total of 200 arrays and microsatellite markers were used in a group of tumors too.
Results: The genotype data of 6206 SNPs located on chromosome 22 with an average distance between SNP of 5.8 Kb was obtained. LOH regions were identified in 15 out of 50 cases combining SNP calls of pair normal and tumor samples. The other two third of cases did not presented any LOH region in chromosome 22. The results were verified using a independent method based on microsatellite markers PCR analysis with 8 markers – D22S535, D22S929, nf2CAV, D22S1172, D22S1162, D22S1156, D22S417 and D22S1056 – located in MN1(22q12.1), NF2 (q12.2), LARGE (q12.3), CARD10 (q13.1), FAM152B (q13.2), POLR2F-SOX10 (q13.1), A4GALT (q13.2), ARHGAP8 (q13.31) and TTL8 (q13.33) genes, in a subset of 15 tumors. LOH frequency were higher with PCR microsatellite study than SNP-arrays and both techniques present a high concordance. All cases were informative for more than half of the microsatellite markers analyzed (>5 loci to 11 loci)
Conclusions: In summary, SNP approach allowed extensively map LOH region of chromosome 22 in meningioma tumors. In contrast to diploid tumors (only one present LOH in 1 locus) LOH was a frequent finding in meningiomas with chromosome 22 losses.

8738 POSTER

Efficacy of glycopeptide cancer vaccine with adjuvants for treatment of intracranial transplanted melanoma B16

O.V. Mazur[1], V.O. Schlyakhovenko[1], S.V. Olishevsky[1], O.Y. Glavacky[2]. *[1]R.E. Kavetsky IEPOR National Academy of Sciences of Ukraine, Tumor Enzymology, Kyiv, Ukraine; [2]A.P. Romodanov Institute of Neursurgery Medical Academy of Sciences of Ukraine, Neurooncology, Kyiv, Ukraine*

Introduction: Despite recent advances in conventional surgical treatment, chemo- and radiotherapy innovative strategies are urgently needed for the successful treatment of brain cancer patients. Consequently, efforts aimed at developing new therapies have focused on new treatment strategies directed on disease elimination, tumor recurrence prevention and inhibition of metastatic dissemination. Cancer vaccines and adjuvants provided the important tools for manipulation of the immunological response to tumors, and therefore can be considered as one of the best alternative to high-toxic conventional anticancer therapies. The main goal of present study was to investigate the efficacy of glycopeptide cancer vaccine (gp50) alone and with adjuvants for therapeutic treatment of intracranial transplanted melanoma B16.
Materials Methods: The gp50 composed of originally prepared autologous 50 kDa-glycopeptide antigens was triply s.c. injected to C57Bl/6 mice with intracranial transplanted melanoma B16. Bacterial CpG DNA (bCpG DNA) and vitamin complex (VC – vitamins C and K_3 in ratio 100:1) were used as vaccine adjuvants. Mice from control group received injections of physiologic saline. The efficacy of immunotherapeutic treatment was evaluated using survival rates of tumor-bearing mice; and cytotoxic activity of splenic lymphocytes and histological examination of changes in mouse brain during vaccinotherapy.
Results: Administration of gp50 alone or combined with bCpG DNA or VC resulted in marked antitumor effect. Median survival rate of mice treated with gp50 alone and combined with bCpG DNA or VC were 27.7 ± 8.0 and 24.6 ± 4.9, 26.0 ± 6.9 days respectively compared with only 13.7 ± 3.8 days in control group. In mice from all treated groups significant increase of lymphocyte cytotoxic activity was also observed. Histological analysis of brain sections showed significant inflammatory lymphocyte infiltrates around tumor masses and necrotizing areas of melanoma cell in brain of mice injected with gp50 alone or with adjuvants as compared with control mice.
Conclusion: Present results suggest that application of gp50 alone or combined with such adjuvants as bCpG DNA and VC can be promising strategy for successful treatment of intracranial tumors.

Lung cancer

Oral presentations (Mon, 21 Sep, 11:00−12:45)

Lung cancer I

9000 ORAL

Mutations of EGFR (mEGFR) in tumour tissue and serum DNA from stage IV non-small-cell lung cancer (NSCLC) patients (p) prospectively treated with erlotinib

R. Rosell[1], B. Massuti[2], M. Cobo[3], A. Sala[4], R. Blanco[5], S. Catot[6], I. De Aguirre[7], C. Queralt[7], C. Mayo[8], M. Taron[1]. *[1]Catalan Institute of Oncology Hospital Universitari Germans Trias i Pujol, Oncology Service, Badalona (Barcelona), Spain; [2]Hospital General de Alicante, Oncology Service, Valencia, Spain; [3]Hospital Carlos Haya, Oncology Service, Malaga, Spain; [4]Hospital de Basurto, Oncology Service, Bilbao, Spain; [5]Hospital de Terrassa, Oncology Service, Terrassa, Spain; [6]Hospital Althaia, Oncology Service, Manresa, Spain; [7]Catalan Institute of Oncology Hospital Germans Trias i Pujol, Oncology Service, Badalona Barcelona, Spain; [8]Pangaea Biotech Institut Universitari Dexeus, Oncology Service, Barcelona, Spain*

Background: We evaluated mEGFR in tumor and matched serum at baseline and assessed their role in a multicenter trial of first- and second-line erlotinib in stage IV NSCLC p with mEGFR in tumor.
Material and Methods: mEGFR were detected in 350 of 2105p (16.6%) screened. 217p with mEGFR received erlotinib; 79 did not due to patient or physician decision. mEGFR were assessed in paired serum samples from 164 p with mEGFR in tumor for whom baseline blood samples were available. mEGFR testing in both tumor and serum was performed centrally. EGFR exon 19 deletions (del 19) were studied by length analysis of fluorescently labeled PCR products and the exon 21 L858R by a PCR Taqman assay.
Results: Overall response rate was 70%, time to progression (TTP) was 14 months (m), and median survival (MS) was 27 m. mEGFR status in the serum matched that in the tumor tissue in 97/164 p (59.1%), in 44.1% of p with PS 0, in 57.4% of p with PS 1, and in 78% of p with PS 2 ($P = 0.01$). There were no differences in the metastatic patterns either according to the presence of mEGFR in serum or according to the type of mEGFR. Response rate was 69.8% in 67 p without mEGFR in serum and 71.7% in 97 p with mEGFR in serum. TTP was 19 m for p with mEGFR only in tumor and 12m for p with mEGFR in tumor and serum ($P = 0.14$). TTP for p with del 19 only in tumor was 22 m vs 13 m for p with del 19 in both tumor and serum ($P = 0.36$). TTP for p with L858R only in tumor was 16 m vs 11