received chemotherapy as primary treatment to postpone irradiation and to minimize its suspected deleterious effects on the growing CNS. Children 5 years and older received EFRT. Upon progression the corresponding treatment modality was applied in a crossover design. Brachytherapy (BT) was used in selected cases regardless of age. The Kaplan–Meier method was used to estimate overall survival (OS) and progression-free survival (PFS). PFS estimates were compared by means of the log-rank test.
Results: During a median follow-up period of 4.3 years (range 0−9.7 years), 59 patients (31%) experienced progression or relapse and 12 patients (6%) died. The 5-years PFS/OS was 60%/92% after EFRT and 69%/94% after BT.
Children with pilocytic astrocytoma achieved a PFS of 69% at 5 years. In contrast, the PFS rate of children with non-pilocytic histology was only 43% ($P < 0.05$).
Neither of the potential risk factors, such as tumour location, prior chemotherapy and age, nor the administered irradiation technique (BT versus EFRT) had a significant impact on PFS.
Escalation of the total dose of EFRT above 45 or 50.4 Gy did not result in an improved PFS.
Conclusions: EFRT plays an important role in the treatment of childhood LGG. In selected cases BT is comparably effective.
Currently the recommended dose prescriptions for EFRT range between 45 and 54 Gy. According to our data a reduction of the total dose below 50.4 or even 45 Gy seems to be feasible without compromising progression-free survival. However the optimal total dose of EFRT still needs to be defined in a prospective trial.
Non-pilocytic histology seems to worsen prognosis.

4101 ORAL

Multicentre Prospective Classification of Childhood Brain Tumours Using Magnetic Resonance Spectroscopy

A.C. Peet[1], T.N. Arvanitis[2], D. Auer[3], R.G. Grundy[4], T. Jaspan[5], L. MacPherson[6], G.S. Payne[7], D. Saunders[8], M. Wilson[9], N.P. Davies[9]. *[1]University of Birmingham, Cancer Sciences, Birmingham, United Kingdom; [2]University of Birmingham, Electronic Elecctrical and Computer Engineering, Birmingham, United Kingdom; [3]University of Nottingham, Academic Radiology, Nottinhgam, United Kingdom; [4]University of Nottingham, Childrens Brain Tumour Research Centre, Nottingham, United Kingdom; [5]University Hospital Nottingham, Radiology, Nottingham, United Kingdom; [6]Birmingham Childrens Hospital, Radiology, Birmingham, United Kingdom; [7]Institute of Cancer Research, Cancer Imaging Centre, Sutton, United Kingdom; [8]Great Ormond Street Hospital, Radiology, London, United Kingdom; [9]University of Birmigham, Cancer Sciences, Birmingham, United Kingdom*

Introduction: Magnetic Resonance Spectroscopy (MRS) provides non-invasive metabolite profiles which can be used to aid diagnosis and provide prognostic markers. Previous studies of MRS for classifying childhood brain tumours have been limited by small numbers of cases and retrospective, single-centre design. The aim of this study was perform a large prospective multicentre evaluation of MRS as a tool for grading childhood brain tumours.
Method: A tool for classifying tumours into low grade vs high grade was built using single-voxel MRS (PRESS, TE/TR 30/1500 ms) acquired using two1.5 T scanners in a single centre (Centre 1) over a 5 year period up to May 2008. A total of 123 cases were accrued with grading confirmed by histopathology (N = 97) or by radiological review with no biopsy (N = 26). Of these, 81 were diagnosed as low grade (LG; WHO grade I or II) and 42 as high grade (HG; WHO grade III or IV). The MRS grading tool was constructed by processing MRS data using TARQUIN to determine metabolite concentrations, this method can account for differences in MRS data acquisition protocols that are difficult to avoid in multicentre studies; then classifier training was performed using principal components analysis followed by linear discriminant analysis. The MRS grading tool was then tested in a prospective manner on data acquired on 6 different scanners in 4 centres. The test dataset consisted of 55 cases from Centre 1 acquired between June 2008 and September 2010, and 55 cases from Centres 2−4, of which 10 were acquired on a 3 T scanner.
Results: The prospective testing gave an overall accuracy of 86%. The classification accuracy of cases from centres 2−4 was lower (80%) than that of cases from centre 1 (92%). Some cases which had an MRS classification of high grade which were low grade on histopathology behaved in an aggressive manner and responded poorly to treatment.
Conclusions: High classification accuracy for tumour grade has been shown in a prospective multi-centre evaluation of a childhood brain tumour classifier based on multivariate analysis of metabolite profiles derived from MRS. Where there is a disagreement between grade given by MRS and histopathology, MRS may aid tumour classification.

4102 ORAL

A Chemical Genetics Screen Identifies a Novel Drug That Targets Steroid Biogenesis and Receptor Signaling Leading to Growth Inhibition of Pediatric Malignant Astrocytoma Cell Lines

D. Poirier[1], N. Ajeawung[2], D. Kamnasaran[3]. *[1]Centre de Recherche du CHUL-CHUQ, Department of Oncology and Molecular Endocrinology, Québec, Canada; [2]Centre de Recherche du CHUL-CHUQ, Pediatric Research Unit, Québec, Canada; [3]Laval University, Department of Pediatrics, Québec, Canada*

Background: Brain tumours are among the leading cause of cancer-related deaths in children, with least 60% manifested as astrocytomas. Malignant astrocytomas represent 8−12% of all pediatric supratentorial brain tumours, with an overall median survival of 11−14 months. While those that arise in the brainstem represent an additional 10−20%, with a 10-year overall median survival of <10%. Despite current therapies, challenges still exist in the treatment of pediatric malignant astrocytomas, leading to the need to explore new therapies. Since a wide range of genes involved in steroid biogenesis and signaling are expressed in pediatric malignant astrocytomas, our objective was to investigate whether novel classes of drugs that target these gene products can be effective in inhibiting growth.
Methods and Results: We screened using a candidate chemical structure approach, a library of 400 drugs which can potentially inhibit steroid biogenesis and cell signaling. By using a panel of human pediatric malignant glioma cell lines established from surgical specimens, we discovered a potent drug that inhibits androsterone (male sex pheromone) biogenesis and with the ability to significantly reduce the viability of pediatric malignant astrocytomas in a dose dependent manner. Cells treated with this drug responded by undergoing apoptosis, cell cycle regulatory, and invasive changes. Furthermore, significant inhibition of transformation was noted. Cells also become increasingly radiosensitive upon drug treatment. Most remarkable, the toxicity on human astrocytes (control) was minimal.
Conclusion: We have discovered a novel drug from a chemical genetic screen which can significantly inhibit the growth of pediatric malignant astrocytomas, with minimal toxicity on non-transformed human astrocytes.

4103 ORAL

Doxorubicin Can Be Safely Omitted From the Treatment of Stage II/III, Intermediate Risk Histology Wilms Tumour − Results of the SIOP WT 2001 Randomised Trial, on Behalf of the SIOP Renal Tumours Study Group

K. Pritchard-Jones[1], N. Graf[2], C. Bergeron[3], B. de Camargo[4], M. van den Heuvel[5], B. Sandstedt[6], J. Godzinski[7], F. Oldenburger[8], H. van Tinteren[9], J. de Kraker[10]. *[1]UCL Institute of Child Health, Molecular Haematology and Cancer Biology, London, United Kingdom; [2]University of Saarland, Paediatric Haemato-Oncology, Homburg, Germany; [3]Institut d'Hemato-Oncologie Pediatrique, Paediatric Haemato-Oncology, Lyon, France; [4]Instituto Nacional do Cancer, Paediatric Haemato-Oncology, Rio de Janeiro, Brazil; [5]Erasmus University, Paediatric Haemato-Oncology, Rotterdam, The Netherlands; [6]Karolinska Institute, Childhood Cancer Research, Stockholm, Sweden; [7]Marciniak Hospital, Paediatric Surgery, Wroclaw, Poland; [8]Academic Medical Centre, Radiotherapy, Amsterdam, The Netherlands; [9]Netherlands Cancer Institute, Biostatistics, Amsterdam, The Netherlands; [10]Academic Medical Centre, Pediatric Haemato-Oncology, Amsterdam, The Netherlands*

Aims: The SIOP WT 2001 trial aimed to test whether doxorubicin (D) can be safely omitted from chemotherapy for stage II/III, intermediate risk histology Wilms tumour (WT), in the setting of exclusion of a newly defined high risk subgroup (blastemal-type) from the randomisation.
Methods: International multicentre trial (28 countries, 261 centres) registering all children diagnosed with a primary renal tumour. Those aged 6m-18 yrs with localized tumours were treated with 4 weeks pre-operative chemotherapy with vincristine (V) and actinomycin D (A). Tumour stage and histological risk group were assigned after delayed nephrectomy. StageII/III intermediate risk WTs were randomized between 26 weeks AV or AVD (total Doxorubicin 250 mg/m^2). Stage III tumours received 14.4 Gy flank irradiation.
Statistics: A non-inferiority limit of up to 10% decrease in 2 yr EFS was considered acceptable. Probability of wrongly accepting non-equivalence was set at alpha 0.025, power 0.90 with recruitment target 550 randomised patients. Randomisation was stratified by participating group and tumour stage.
Results: 583 patients were randomized between 11/2001−12/2009, with 341 stage II and 242 stage III. Median follow up was 39 months. 94% (512/543) were confirmed as eligible by central pathology review. In intention to treat analysis, there were 22 events (20 relapses)/9 deaths among 291 randomised to AVD and 34 events (27 relapses)/7 deaths