Neuropathology

1602 Pathologic Complete Response Is Associated with Good Prognosis in Patient with Pancreatic Ductal Adenocarcinoma Who Received Neoadjuvant Chemoradiation and Pancreatectomy.

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Background: Patients with pancreatic ductal adenocarcinoma (PDA) has poor prognosis. To improve the clinical outcome, most patients with PDA are treated with neoadjuvant chemoradiation prior to surgery at our institution. In this group of patients, pathologic complete response (PCR) is rarely observed in subsequent pancreatectomies. However, the prognostic significance of PCR is not clear.

Design: Among 442 patients with PDA who received neoadjuvant chemoradiation and pancreatectomy from 1995 to 2010, 11 (2%) patients with PCR were identified. The cytologic diagnosis on pre-therapy tumor was reviewed and PCR in pancreatectomies was confirmed in all patients. Clinical and follow-up information were extracted from the medical records. Survival analysis was performed using the Kaplan-Meier method.

Results: There were 6 men and 5 women with age ranging from 43y to 75y (median: 61y). 4/11 (36%) patients had prior history of or synchronous extrapancreatic cancers, including one with lung cancer, one with breast cancer, one with prostate cancer and one with renal cell carcinoma. 5 patients received neoadjuvant chemotherapy followed by chemoradiation and 6 patient received chemoradiation. 10 patients had pancreaticoduodenectomy (PD) and one had distal pancreatectomy. These specimens were well sampled by histology and the entire pancreas was submitted for histology in 9 cases. On review, scar with fibrosis and chronic pancreatitis were present in all eleven cases. Carcinoma in situ was present in 2 cases and PanIN3 or PanIN2 in 4 cases. However, no residual viable invasive carcinoma cells or lymph node metastasis was identified in all cases. Follow-up information was available in 9/11 patients. Follow-up time ranges from 6M to 181M (median, 49M). During follow-up, four patients died, including one from brain metastasis of prior lung cancer, one from bone metastasis of breast cancer, one from sepsis, and one developed a second primary or recurrent PDA in the tail of pancreas at 84 M after PD and died of PDA at 105 M after the diagnosis of the initial PDA. The last patient had carcinoma in situ in the initial PD specimen. The other 5 patients were alive with no evidence of disease. Patients with PCR had better survival compared to the 240 patients who had residual viable PDA in pancreatectomy specimens after neoadjuvant therapy (p<0.001).

Conclusions: Patients with PDA who received neoadjuvant chemoradiation and had PCR in pancreatectomy is rare and is associated with better prognosis.

1603 Hepatocellular Carcinomas Occasionally Express Neuroendocrine Markers While Neuroendocrine Tumors Metastatic to the Liver Do Not Show Hepatocellular Expression.

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Background: Neuroendocrine tumors (NETs) of gastrointestinal tract are generally slow growing but frequently metastasize to the liver, ranking second to colorectal carcinoma as a source of liver metastases. Distinction between NET and hepatocellular carcinoma (HCC) can be challenging on a small biopsy because both can show nested and trabecular patterns. In addition, immunostaining for neuroendocrine markers has been observed occasionally in HCCs. Utilizing immunohistochemistry for hepatocyte, glypican-3, CD56, synaptophysin (Syn) and chromogranin A (Chr), we analyzed the staining profile in HCCs and NETs to determine how often the tumors show an overlapping pattern of expression.

Design: Tissue microarrays were constructed from formalin-fixed, paraffin-embedded blocks of 48 NETs metastatic to the liver and 114 HCCs from our archives and stained for hepatocyte, glypican-3, CD56, Syn and Chr. Immunostaining was evaluated by two pathologists; > 5% immunoreactivity was considered positive and intensity was scored for each (1+, weak; 2+, strong).

Results: Of the 114 HCCs, 107 (94%) were positive for hepatocyte or glypican-3, 92 (81%) for hepatocyte, 67 (59%) for glypican-3, and 52 (46%) for both. Seven HCCs (6%) showed positivity for CD56 (4 focal, 3 diffuse, 2 weak and 5 strong), of which 3 (3%) were also positive for Syn (all focal, 1 weak and 2 strong). All 7 HCCs positive for CD56 or Syn expressed hepatocyte or glypican-3 and none were fibrolamellar type. None of the HCCs expressed Chr. All 48 NET liver metastases expressed at least one neuroendocrine marker. All but one (98%) NETs were positive for Syn, 40 (83%) for Chr and 39 (81%) for CD56. Thirty-four NETs (71%) expressed all neuroendocrine markers. No hepatocyte or glypican-3 expression was present in the NET liver metastases.

Positive immunostaining in HCCs and NETs metastatic to the liver

	Hepatocyte	Glypican-3	Synaptophysin	Chromogranin A	CD56
HCC (n = 114)	92	67	3	0	7
NET (n = 48)	0	0	47	40	39

HCC, hepatocellular carcinoma; NET, neuroendocrine tumor.

Conclusions: Occasional HCCs express CD56 and Syn, while all express either hepatocyte or glypican-3. NETs metastatic to the liver do not express hepatocyte or glypican-3 and almost always express Syn, while Chr and CD 56 are seen in most cases. Utilizing a limited immunohistochemistry panel, including hepatocyte, glypican-3, Syn and Chr, can efficiently distinguish HCC from NET liver metastases and help avoid diagnostic pitfalls on small biopsies.

1604 Nestin, an Important Marker for Differentiating Oligodendroglioma from Astrocytic Tumors.

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Background: Nestin is an acronym for neuroepithelial stem cell protein. It is an intermediate filament protein expressed in proliferating cells during the developmental stages in a variety of embryonic and fetal tissues. It is also expressed in some adult stem/progenitor cell populations, such as newborn vascular endothelial cell. Differentiation between astrocytic tumors and oligodenoglioma tumor is of paramount importance because of different lines of treatment and different prognosis.

Design: We performed Nestin immunostaining on paraffin blocks of 16 cases of astrocytomas of various grades (3 Glioblastoma, 3 anaplastic astrocytoma, 3 fibrillary astrocytoma and 7 Pilocytic astrocytoma) and on 12 oligodendroglioma (6 grade II, and 6 grade III). All cases of oligodendroglioma has confirmation by FISH for 1p 19q.

Results: Nestin staining was seen in all astrocytic tumors. The strongest staining was in glioblastomas and in Anaplastic astrocytomas.
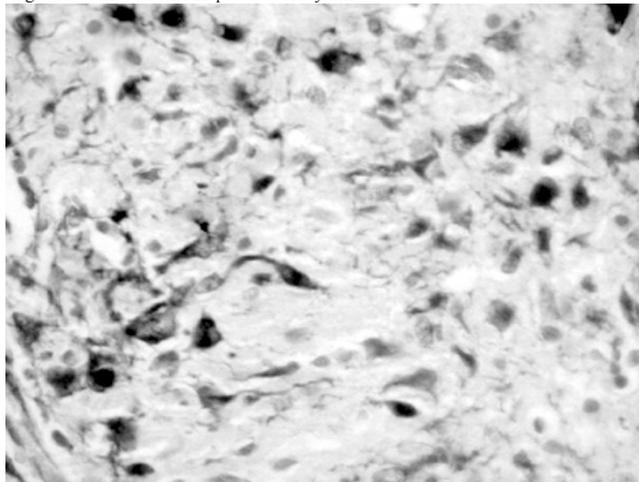
Pilocytic astrocytomas show mostly focal and weak staining with strong staining of Rosenthal fibers. Grade II astrocytoma shows weak but more intense staining than pilocytic astrocytoma. No Nestin immunostaining was seen in any of the oligodendroglioma tumor cells, but Nestin stained the endothelial cells in oligodendroglioma as a positive internal control.
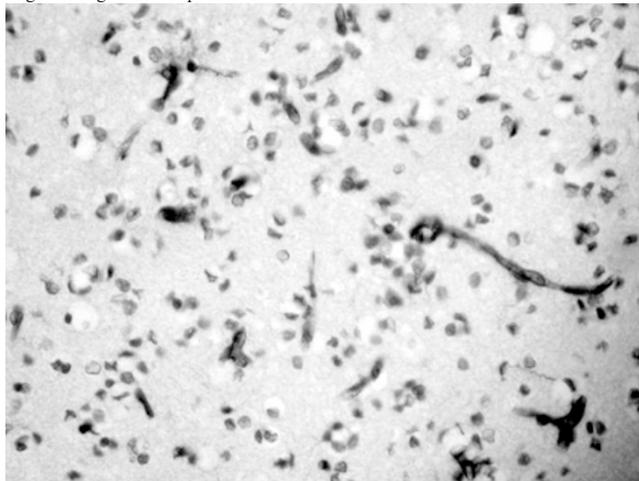
Conclusions: Nestin is an important immunohistochemical marker in differentiating oligodendroglioma from astrocytic tumors. Nestin, also, is helpful in grading astrocytoma.

1605 Analysis of Glioma Stem Cell Markers and Genomic Alterations in Primary and Recurrent Glioblastomas.

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Background: Glioblastoma (GBM) is an aggressive primary CNS tumor, with a median survival of one year following standard therapy. Previous studies demonstrated an association between the glioma stem cell (GSC) compartment and biologic aggressiveness. Moreover, recurrent post-radiation GBMs are enriched for GSCs in animal models. Here we investigate whether stem cell markers are increased in recurrent human GBMs compared to the primary and also examine whether genetic alterations are associated with the expression of GSC markers.

Design: Primary and recurrent GBMs from 13 patients (29-67 yrs-old; 4F, 9M) were included. Paraffin-embedded slides were stained for CD133, Sox2, Nestin, c-Myc and

p53. FISH was performed for *EGFR* status. Immunohistochemical (IHC) staining for p53 was ranked as positive or negative. Quantification of CD133, Sox2, Nestin and c-Myc staining involved counting positive cells in 10 HPFs (40x), with intensity graded on a scale of 0-4, and then calculating an H-score. IHC and FISH results were compared with clinical parameters (age, gender, time to tumor recurrence) and analyzed for correlations. A rank sum test and the t-test were used to determine statistical significance.
Results: No statistically significant difference was noted in CD133, Sox2, Nestin or c-Myc staining in primary and recurrent GBMs. Expression of p53 was noted in 6/12 primary GBMs (50%). *EGFR* was amplified in 5/13 (38%). GBMs with EGFR amplification trended toward a higher H-score for Sox2 (mean = 2.8) than non-amplified cases (mean = 2.2; p = 0.06). P53 expression was not associated with differential c-Myc, CD133, Sox2 or Nestin expression. GBMs with high c-Myc expression (H > 0.9) recurred more quickly (mean = 9.4 mos) than those with lower expression (mean = 20 mos). Large increases in c-Myc expression (>75%) were associated with short recurrence intervals (p = 0.06).
Conclusions: In human GBMs, tumor cells expressing c-Myc, CD133, Nestin and Sox2 are not substantially increased in tumor recurrences. However, primary GBMs with high c-Myc expression and tumors with the greatest change in c-Myc expression from primary to recurrence had the shortest recurrence intervals. An association was noted between EGFR amplification and SOX2 expression.

1606   Immunohistochemical Assessment of Neuroepithelial Markers and Hamartin/Tuberin Expression in Subependymal Giant Cell Astrocytoma (SEGA): Further Evidence for Ambiguous Differentiation and mTOR Signal Transduction Dysregulation.
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Background: The exact nature of subependymal giant cell astrocytoma (SEGA) has been debated due to evidence of divergent differentiation and the uncertainty about the cell of origin. Mutations and subsequent biallelic inactivation of either *TSC1* encoding hamartin, or *TSC2* encoding tuberin have been demonstrated in SEGAs. This inactivation is suggested to lead to the loss of proteins that inhibit mammalian target of rapamycin (mTOR) disrupting a large number of tightly regulated cell functions.
Design: In order to determine their practical diagnostic value and help in identifying the mutated protein, we analyzed the expression of tuberin and hamartin proteins as well as neuroepithelial markers in 9 patients with SEGAs. In addition, RPS6 and 4EBP1 regulatory proteins that are downstream to the heterodimer in the mTOR pathway were also evaluated. Normal brain tissue and other glial tumors obtained from neuropathology files were used as controls.
Results: Hamartin and tuberin expression levels were found to be relatively decreased in the SEGA specimens when compared to controls, while the expression levels of RPS6 and 4EBP1 were increased. Interestingly, GFAP was strongly positive in only 5 of the cases (in addition to 3 negative and 1 weakly positive), while Synaptophysin positivity was found in all tumors. Staining for CD34 (a marker often observed in well differentiated glioneuronal tumors) and Olig2 (a nuclear marker present in most gliomas) were entirely negative in all tumor cells. Ki67 (MIB-1) showed a low proliferation rate ranging from 2% to 8%.
Conclusions: Our results suggest that staining for either hamartin or tuberin is unlikely to be of diagnostic value due to positivity in almost all tumors and normal tissues, even if the expression is relatively decreased in SEGAs as expected. Increased expression of RPS6 and 4EBP1 further confirms the activation of mTOR pathway and the possible role these molecules may have in the growth of these tumors. Staining with neuroepithelial markers further supports the suggestion of ambiguous differentiation. SEGAs do not appear to have the typical expression profiles of astocytic tumors, under which they have been classified.

1607   i17q REPA/REPB Rearrangement in Medulloblastoma: A Marker for Early Recurrence.
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Background: Medulloblastoma is the most common malignant brain tumor in children, accounting for 20 percent of all pediatric central nervous system tumors. Despite its relatively high incidence, the biology of this entity is poorly understood. Diagnosis is made based on histology, and prognosis is dependent on staging, tumor size, and age of onset. However, clinical factors do not accurately predict which standard-risk patients will have early relapse and die. Outcome is believed to be influenced by grading and the presence of certain molecular markers, including the i17q chromosome. i17q has been shown to correlate with poor prognosis; however, data demonstrating that it is of prognostic value independently of anaplasia are lacking. In a majority of cases, i17q is not a true isochromosome but an isodicentric chromosome (idic(17)(p11.2)), with rearrangement breakpoints within the REPA/REPB low-copy repeat element region in 17p11.2. Low-copy repeat elements are large DNA elements (larger than 1 kb) with greater than 90% homology that facilitate rearrangements by non-allelic homologous recombination. We recently described a FISH-based approach to identify this rearrangement in medulloblastoma and showed it to be both sensitive and specific compared with G-banding analysis.
Design: Using our FISH-based assay, we analyzed 60 consecutive cases of medulloblastoma for the presence of i17q. All cases had a minimum 5-year clinical follow-up. The presence of of i17q, idic(17)(p11.2), and histological grade were compared to the clinical outcome.
Results: 14 (23%) of the cases had i17q, with 10 (17%) having the common rearrangement. All groups, regardless of grade or stage, had worse outcomes with the presence of i17q. Of the standard-risk patients, tumors with i17q had remission, recurrence, and mortality rates of 33%, 67%, and 42%, compared to 54%, 43% and

31%, for those without. Mean time to recurrence and time to mortality were 23.75 and 17.6 months compared to 49.0 and 55.5 months, respectively. Tumors with the common rearrangement had remission, recurrence, and mortality rates of 30%, 70%, and 40%. At five years' post diagnosis, nearly 70% of standard risk patients without i17q were disease-free compared to 45% with the rearrangement. No correlation was present between anaplasia and i17q.
Conclusions: Medulloblastoma patients with i17q have worse outcomes than those without, independent of tumor grade. Our test for i17q may be useful to identify average-risk patients who are more likely to have early relapse.

1608   MGMT Promoter Methylation in Gliomas. Comparison of Methods: Methylation Specific PCR (MSP) vs Pyrosequencing.
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Background: Methylation of MGMT gene promoter is predictive of response to alkylating chemotherapy and a prognostic biomarker for improved survival in patients affected by glioma and treated with radiotherapy combined with temozolomide. MGMT promoter is methylated in about 40% of primary glioblastomas and also low levels of methylation predict pharmacological response. Therefore testing for MGMT promoter methylation is increasingly performed as routine test in neuropathology laboratories. MSP was introduced firsty and is still the most popular assay, however other quantitative techniques have been then developed. The aim of our study was to compare a qualitative and a quantitative method for MGMT promoter methylation status, i.e. MSP and Pyrosequencing.
Design: A total number of 119 cases of gliomas have independently been tested by means of MSP and Pyrosequencing at 2 different laboratories. All samples were from formalin-fixed and paraffin embedded tissues. After DNA extraction, conversion of unmethylated cytosines to uracils has been carried out. MSP was performed following the directions published elsewhere. For all cases a quantitative PCR assay (MS-qPCR) was applied to confirm MSP results. Pyrosequencing was done using a commercially available kit (PyroMark™ MGMT kit, Qiagen) according to manufacturer's instructions on a PyroMark™ Q96 ID instrument (Qiagen). The test is designed to detect and quantify methylation level in five CpG sites in exon 1 of MGMT gene.
Results: Concordance between MSP and Pyrosequencing has been observed in 114/119 (96%) cases. Four patients evaluated by MSP techniques revealed non-amplifiable DNA, while all but 1 case analysed by Pyrosequencing gave a diagnostic DNA. Pyrosequencing internal control for bisulfite treatment always showed complete conversion. Only 1 case was unmethylated by MSP while Pyrosequencing showed methylation status. Eight cases gave discordant results, but after test repeating Pyrosequencing demonstrated correct results.
Conclusions: Our study indicates that the yield of MSP and Pyrosequencing is highly comparable, however Pyrosequencing has the added value of quantifying the methylation status of single CpG islands. Furthermore it allowed identification of very low levels of methylation even in single CpG sites.

1609   Embryonal Malignant Neuroepithelial Tumors of the Cerebellum with No Neuroblastic Differentiation: Medulloblastoma Variant or Different Entity?
B Ellezam, V Mehta, GR Courteau, AM Adesina. Texas Children's Hospital, Baylor College of Medicine, Houston.
Background: Medulloblastomas are embryonal small blue cell tumors with predominantly neuroblastic differentiation. Distinction from small cell variants of other tumor types is dependent on immunophenotype and ultrastructural characteristics. A minor subset of embryonal malignant neuroepithelial tumors occur in the cerebellum and show no demonstrable neuroblastic, glial or epithelial differentiation. These tumors remain poorly characterized and their relationship to classic medulloblastoma and variants in terms of tumor biology and prognosis is unclear.
Design: Surgical pathology records of patients operated at Texas Children's Hospital between 1995 and 2010 were searched for embryonal cerebellar tumors with small cell morphology. Medulloepitheliomas, small cell glioblastomas and ATRTs were not included in this study. Malignant embryonal neuroepithelial tumors with no evidence of neuroblastic differentiation by histology, immunohistochemistry and electron microscopy were identifed and processed for additional molecular studies as well as review of outcome. Analysis for copy number aberrations were done by array CGH and FISH. Results were compared to those previously reported for medulloblastoma and other embryonal cerebellar tumors.
Results: A total of 98 small blue cell cerebellar tumors were identified with only 2 cases meeting the defined criteria for undifferentiated malignant embryonal neuroepithelial tumors. Treatment included gross total resection of primary tumor, followed by chemotherapy and craniospinal radiation therapy, as per protocol for standard high-risk medulloblastomas. FISH analysis did not reveal amplification of *C-MYC, N-MYC, EGFR* or *OTX2*. No deletion of INI1/HSNF5 locus or monosomy 22 was identified. Array CGH revealed multiple loci and gene-specific copy number aberrations that did not mimic those previously described for medulloblastoma. No isochromosome 17q was identified. In spite of dissemination at presentation, one patient is alive and well after four years and the other has only had a soft tissue surgical site recurrence which was successfully excised one year after initial surgery.
Conclusions: Cerebellar embryonal malignant neuroepithelial tumors with no neuroblastic differentiation show differing molecular signatures from those of medulloblastoma with implications for possible differing tumor biology and prognosis.

1610 Gliosarcomas, a Review of Clinicopathological Features of a Series of 28 Cases – An Institutional Experience.
S Epari, S Ahmed, V Tiwari, A Moiyadi, R Jalali, P Shetty, T Gupta, M Bal, S Kane. Tata Memorial Centre, Mumbai, Maharastra, India.
Background: Gliosarcomas (GS) are rare WHO grade IV primary biphasic brain tumours composed of high grade glial and mesenchymal components.
Design: Achives of the departmental files of the last five years were reviewed and cases of gliosarcoma, where paraffin blocks and reasonable clinical information were available were included.
Results: Total number of 28 cases with age range of 32-70 yrs (median: 50yrs and mean: 51 yrs) and sex ratio: 3:1(M- 24; F-4) were noted. The location of these tumours were predominantly cerebral hemispheric with commonest being temporal (n-11). Other sites are – frontal: 9 (including one case of frontoparietal), parietal: 4, occipital:2, hippocampal with a predominant intraventricular:1 and posterior fossa :1 (predominant component is in cerebellopontine [CP] angle). One case each occurred in treated patients of medulloblastoma and adenoid cystic carcinoma of lip. Histologically, all except for one case showed an intricate admixture of glial and mesenchymal components. One case (known treated case of adenoid cystic carcinoma) showed a predominantly sarcomatous component with very scant (<5%) glial component. In six of the cases, the sarcomatous component showed myogenic differentiation (smooth muscle actin and calponin, both positive), one case showed chondrosarcomatous differentiation and in rest of the cases the differentiation of the sarcomatous component could not be made. Additionally, three cases showed admixed population of small undifferentiated small cell component (Mic-2 was negative in all of these cases). In two of the cases, an epithelioid morphology was noted (both epithelial membrane antigen and pancytokeratin were negative). p53 protein immunopositivity was noted in 26 cases; it was negative in two cases (one of which showed round cell component). MIB-1 labeling index (LI) was variable 15-40% (10-20% -22, 20-30% -3 and 30-40% – 3). One case showed extracranial metastasis (p53 negative, comprising a component of undifferentiated small cells) to iliac bone.
Conclusions: GS are rare primary brain tumours, this series documents the occurrence at rare sites (in intraventricular and CP angle), as second primary tumours in a previously diagnosed unrelated malignancies, heterogeneity of dedifferentiation (undifferentiated, myogenic and rare matrix producing chondrosarcomatous) and their potential for extracranial metastases.

1611 Pilomyxoid Astrocyoma: Report of Fourteen Cases with Clinicopathological Features.
S Epari, P Patil, V Tiwari, R Jalali, A Moiyadi, T Gupta, M Bal, P Shetty, S Kane. Tata Memorial Centre, Mumbai, Maharashtra, India.
Background: Pilomyxoid astrocytoma (PMA) recently recognized as a distinct grade II entity in WHO 2007 Central nervous system tumours classification.
Design: Sixteen cases were retrieved from the department files of last five years.
Results: Of the sixteen cases, two were excluded (one case was revised to an anaplastic astrocytoma while the other due to lack of paraffin blocks). The rest 14 cases formed the study sample, which were seen in 9 males and five females. Ten presented before 16 years of age (≤10 yrs: 7, 10-16 yrs: 3); rest at 18, 20, 31 and 32 years respectively. The predominant cases (6 cases) were in suprasellar region. Other sites are posterior fossa: 4 (cerebellum- 3, 4rth ventricle: 1), 3rd ventricle – 2, and cerebral hemisphere -2 (one each in left fronto-parietal and parieto-occipital). Radiologically, they are homogenously enhancing circumscribed tumours without perilesional edema. All cases histologically showed oval to elongated oval shaped tumour cells in a diffuse myxoid fibrillary matrix background. Focal areas of relative increased cellularity noted in 10 cases and additionally 8 of the cases showed presence of areas of focal condensation of tumour cells around blood vessels. Biphasic architecture, Rosenthal fibres, eosinophilic granular bodies, mitotic activity, microvascular proliferation and necrosis were not seen in any of these cases. Immunohistochemically, all cases showed diffuse and strong positivity for glial fibrillary acidic protein; while negative for epithelial membrane antigen (EMA), synaptophysin and p53. MIB-1 labeling index was 1-3% in 9 cases, 3-4% in 4 cases and 6-8% in 1 (one of the cerebral hemispheric lesion). Gross total resection was achieved in 5 cases (cerebellar-2, cerebral hemispheric -2 and 4rth ventricle -1). Radiation was received in 9 cases. Follow-up data (varying from 6 months to 40 months) was available for nine cases, one case (cerebellar location) showed local recurrence after a period of 11 months and two cases (both of them of suprasellar location) showed spinal drop metastases after 10 and 15 months of surgery respectively.
Conclusions: PMA is a distinct entity, characterized by the lack of typical features of pilocytic astrocytoma. In addition, it appears PMAs tend to exhibit a relative aggressive biological behavior with a relative higher incidence for spinal deposits, which needs to be confirmed in a larger study with an adequate follow-up period.

1612 Pathological Characteristics of Pediatric Intracranial Pilocytic Astrocytomas and Their Impact on Outcome in Three Geographically Distinct Regions: A Multi-institutional Study.
A Ersen, T Tihan, I Qaddoumi, M Alsughayer, S Ozuysal, M AlHoussaini, A Baneerjee. Dokuz Eylul University, Izmir, Turkey; University of California San Francisco; St Jude Children's Research Hospital, Memphis, TN; King Hussein Cancer Center, Amman, Jordan; Uludag University, Bursa, Turkey.
Background: Pilocytic astrocytoma (PA) is one of the most common neoplasms in children and total resection is often curative. The significance of many clinical and pathological features as well as the cell of origin of PAs are still unclear. Furthermore, some authors suggest different survival characteristics of PA in different regions, which could significantly affect the results of multinational studies, if validated. The number of such studes is alarmingly limited to provide an insight on this issue.

Design: In an attempt to determine the significance of clinicopathological features on outcome and the expression patterns of stem cell markers, we studied all PAs from four institutions during a 10 year period. All intracranial PAs with sufficient clinical information and tissue were included. Spinal tumors and tumors with pilomyxoid features were excluded. Immunohistochemical analyses were carried out in tissue microarrays as well as whole slides, and included EGFR, neurofilament, caspase3, bcl-2, CD34, CD44, synaptophysin, vimentin, GFAP, CD133, p75NTR, Sox2, Olig2, p53, MIB-1, Neu-N, BRAF, nucleostemin.
Results: 116 patients fulfilled the inclusion criteria (65 males, 51 females). Both event-free and overall survival were significantly better in patients who underwent gross total resection. There was a significant survival difference among institutions. Among the stem cell markers tested, only Sox2 had significant staining in 43% of tumors. All tumors were positive with GFAP and Olig-2 while 23 cases had positive Synaptophysin staining. Median MIB-1 proliferation index was 2%. BRAF was positive in most tumors but the staining was more prevalent and stronger among tumors in the posterior fossa. We found no significant effect of any of the markers or NF-1 status on event-free survival.
Conclusions: Positive immunostaining with Sox2 suggests that PAs may be related to stem cells expressing Sox2. Extent of resection and age are significant prognostic factors for recurrence. Adjuvant treatment did not appear to provide any benefit in subtotally resected tumors. Significantly different survival probability among institutions poses significant difficulties in interpretation.

1613 EGFR/HER1 Isoforms Expression in Gliomas.
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Background: The *EGFR* gene encodes four different mRNAs generated by alternative splicing, the variants 1 to 4. Variant 1 mRNA generates the receptor isoform a, better known as EGFR or HER1, which consists of three domains, extracellular, trans-membrane and intracellular. Variants 2, 3 and 4 mRNAs respectively translate in isoforms b, c and d, three soluble receptors without intracellular domain. A mutant, *EGFRvIII*, have been reported in glioblastomas which differs from EGFR in a truncated extracellular domain. The role of the soluble receptors remains greatly unknown and their expression has never been studied in gliomas.
Design: EGFR variant 1, 2, 3 and 4 mRNAs were quantified by RT-PCR in 29 adult infiltrative gliomas (4 astrocytomas, 9 glioblastomas, 4 oligoastrocytomas and 12 oligodendrogliomas). Primer pairs were designed to amplify separately variant 2, 3 and 4 transcripts but variant 1 and EGFR vIII mRNAs together (variant 1+vIII). The relationship between variant mRNA levels and tumor types, *EGFR* gene amplification and EGFR protein expression detected by immunohistochemistry (IHC) was studied. For IHC analysis, we used two antibodies: one, targeted against the extracellular domains, bound the isoforms a, b, c, d and the EGFRvIII (Ext-Ab); the second one, targeted against the intracellular domain, labeled isoform a and EGFRvIII (Int-Ab). Immunoexpression was scored as no/weak for less than 50% of labeled tumor cells and strong for more than 50%.
Results: Transcripts of variants 1+vIII, 2, 3 and 4 were expressed in gliomas and their expression was strongly linked (p<0.0001). However, variants 3 and 4 were significantly overexpressed in glioblastomas (p=0.04 and p=0.03, respectively). Tumors with *EGFR* gene amplification expressed higher levels of variants 2, 3, and 4 transcripts (p=0.05, p=0.007 and p=0.02 respectively) than tumors without. The Ext-Ab labeled a higher number of tumor cells than the Int-Ab (p<0.0001). There was a positive correlation between variant 1+vIII mRNAs levels and EGFR protein expression detected with the Int-Ab (p=0.04). This link was not found with the Ext-Ab since it recognized the soluble isoforms in addition to isoforms a and mutant vIII.
Conclusions: EGFR/HER1 and EGFRvIII are not the sole isoforms expressed in gliomas. Other EGFR/HER1 variants, whose mRNAs encode soluble isoforms of the receptor, are strongly expressed in these tumors, notably in glioblastomas. Their expression should be taken into consideration when interpreting the results of the immunohistochemical analysis and to evaluate or seek treatments targeted against EGFR.

1614 Meningioangiomatosis: The Pathological Spectrum of Lesions in Four Cases Including the First Report of a Fetal Case.
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Background: Meningioangiomatosis (MA) is a rare, benign intracortical proliferation of meningothelial-like and fibroblast-like cells and vessels. It occurs in children and young adults with epilepsy. MA is more frequently sporadic than associated with NF2. MA is exceedingly rare in children under 3 years of age, and to date any case has been previously reported in a fetus. We have evaluated the clinicopathological characteristics of four cases, including the first reported case in a fetus, which illustrate the phenotypical diversity of this entity.
Design: We studied the clinical findings and surgical specimens of sporadic MA from three male patients (10, 16, 24 years) with a history of intractable seizures and the brain at autopsy of a 22-week-old male fetus. Clinical, neuroimaging and histopathological features, including immunostains for EMA, SMA, CD34, NeuN, Tau, betaA4, alpha-synuclein, TDP43, ubiquitin, and MIB-1, were evaluated.
Results: All the lesions were located in the frontal lobes and were heavily calcified except the fetal case. Microscopically, an extra-axial component made up of fascicles and whorls of fibroblastic-like cells with hyalinisation and calcification, and an intra-axial component with profuse vascular proliferation and perivascular meningothelial-like cells invading the brain were observed. In spite of the meningothelial-like morphology of perivascular cells, EMA staining was negative in all the cases. CD34 was positive in three lesions and SMA in two. The MIB1 LI was <0.1% in the four cases. Entrapped

neurons demonstrated abundant tau+ (AT8+, 3R+, 4R+) neurofibrillary tangles and threads, especially in the three oldest patients.

Conclusions: MA is a rare, slow-growing meningocerebral lesion which neoplastic nature, histogenesis, and pathogenesis remain elusive. We report the first case in a fetus. Although morphologic features suggest a meningothelial differentiation, the inconstant immunostaining profile does not support this hypothesis. The lesion may be misinterpreted as an invasive meningioma, vascular malformation, astrocitoma or glioneuronal tumour, especially in the absence of adequate clinical information. The degenerative changes in the intervening cortex and calcification could be related to the age of the lesion.

1615 Genomic Changes in Gliomas by Single Nucleotide Polymorphism (SNP) Array in Formalin-Fixed Paraffin-Embedded (FFPE) Tissue.
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Background: In oligodendrogliomas (ODG), genomic changes in chromosomes 1p and 19q have diagnostic, prognostic and therapeutic implications. Currently, deletion or loss of heterozygosity (LOH) is identified clinically by fluorescence *in situ* hybridization or short tandem repeat (STR or microsatellite) analysis. These assays suffer from the limitation that the probes or primers interrogate only small portions of the chromosomes. In this study, we investigated the use of SNP array for identifying genomic changes in gliomas utilizing DNA extracted from FFPE tissues.
Design: Genomic DNA was extracted from FFPE tissues of 14 brain tumor cases [7 ODG and 7 non-ODG]. DNA quality was determined using BioScore Screening and Amplification Kit. DNA from each tumor was run on the Illumina SNP array with 300K markers. The data were analyzed using Illumina KaryoStudio. SNP array results were compared with our standard clinical STR assay of chromosomes 1p and 19q. SNP array abnormalities of other chromosomes were also identified and the results were compared with the pathological diagnoses.
Results: Quality of DNA from FFPE samples correlated well with SNP array data quality; higher quality DNA had a smaller variance. Nevertheless, all data were interpretable. Seven ODG cases had LOH by STR and deletion or LOH by SNP array on both 1p and 19q. Two astrocytoma (AC) cases had no evidence of LOH or deletion and two other cases (1 anaplastic AC and 1 glioblastoma) had 19q LOH alone by both assays. Three cases had segmental deletions or LOH of 1p and/or 19q by array that were not detected by STR analysis. The final diagnosis of these three cases was anaplastic AC. There was no major discordance between SNP array and STR results with the added advantage that SNP array can distinguish between deletion and copy neutral LOH. The number of other chromosome abnormalities was higher in high grade gliomas [3.4±0.8 in Grade II (n=5), 8.0±1.6 in Grade III (n=7) and 12.0±1.0 in Grade IV (n=2)].
Conclusions: Assessment of genomic changes in gliomas using SNP array to analyze FFPE samples is feasible and has great potential for an accurate clinical diagnostic test. Small deletions or LOH that may be missed by the current assays are detectable by SNP array. The clinical significance of these small deletions, copy neutral LOH and abnormalities on other chromosomes has yet to be determined and will require further studies.

1616 Angiocentric Glioma: Is It Really WHO Grade I?
KK Hooper, JM Osman, SM El Jamal, AG Saad. Arkansas Children's Hospital, Little Rock.
Background: Angiocentric glioma (AG) is a recently described brain tumor and is recognized by the 2007 WHO classification of central nervous system as a grade I tumor. AG is characterized by slow growth and typically presents with seizures in children and young adults. The cytogenesis remains unclear; however, ependymal and glioneuronal origins have been proposed.
Design: Three AGs are included in this study [two AGs were retreived from the files of the department of Pathology at Arkansas Children's Hospital (from 1995 and 1998, respectively) which were interpreted then as pilocytic astrocytoma]. A third case was received in 2009. Demographic and clinical findings were retrieved from medical records.
Results: Histologically, the tumors were characterized by diffuse growth and prominent perivascular tumor cell arrangements with features of astrocytic/ependymal differentiation. Rosenthal fibers and eosinophilic granular bodies were absent. Necrosis and vascular proliferation were not observed and mitoses were sparse or absent. On follow up (mean 31.3 months; range 14-49 months), one patient had 2 recurrences, another had 3 recurrences and one patient is still disease-free 14 months after surgery. The 1st recurrence occurred after a mean period of 10 months (range: 9-11 months) and the second recurrence occurred after a mean period of 19.5 months (range 19-20 months). The 3rd recurrence occurred 32 months after the first surgery. Histologic examination showed that recurrences were not accompanied by progression of tumor grade or MIB-1 labeling indices. A summary of the clinical and demographic findings is presented in Table 1.

Table 1: Demographic and clinical findings of patients with angiocentric glioma

Case	Age (years)	Sex	Location	Clinical presentation	Follow-up	Ki 67 labeling index	Extent of surgery
1	6.7	M	Frontal	Seizures	2 recurrences at 11 and 19 months after 1st surgery, respectively	2, 2 and 3%, respectively	Total gross resection
2	10.3	M	Temporal	Seizures	3 recurrences at 9, 20 and 32 months after 1st surgery, respectively	1, 3, 2, and 5%, respectively	Total gross resection
3	13.9	F	Temporal	Seizures	Disease-free 14 months after surgery	2%	Total gross resection

Conclusions: We present 3 cases of AGs. Follow up showed that 2 patients presented with multiple recurrences and the one patient is still disease-free. While we did not find any difference in tumor histology or MIB-1 labeling index, our data suggest that AG run a clinical course that is unusual for a WHO grade I tumor. Additional studies with larger number of patients are required to further study this observation.

1617 Primary Hematolymphoid Lesions of the Meninges: A Clinicopathologic Study of 9 Cases Presenting as Mimics of Meningioma.
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Background: Primary hematolymphoid lesions of the meninges are rare and only a few cases have been reported in the English literature. We report our experience with primary meningeal hematolymphoid neoplasms and review their clinicopathologic spectrum.
Design: 9 primary meningeal hematolymphoid lesions were identified in our database from 2000-2010. The histopathologic features were reviewed along with clinical, laboratory and imaging data. Primary meningeal lesions were defined as those with meningeal association by imaging or histology and no prior diagnosis of lymphoma or leukemia.
Results: Of 9 cases reviewed, the patient ages ranged from 30 to 59 years old (mean 40 years) and males predominated [5:4]. All cases except one were non-Hodgkin lymphoma (NHL). Subtypes of NHL included 4 cases of diffuse large B-cell lymphoma (DLBL), 3 cases of marginal zone lymphoma (MALT) and 1 case of Burkitt-like lymphoma. The remaining case was Castleman's disease, plasma cell variant, which arose in the setting of panhypopituitarism. 8 cases presented with imaging studies mimicking meningioma, while one case (DLBL) presented with imaging which resembled discitis. None of cases were associated with prior or subsequent central nervous system (CNS) neoplasms. One case (MALT) had prior chemotherapy and radiation for glassy cell carcinoma of the uterine cervix. One case (Burkitt-like lymphoma) had a prior CNS abnormality (Chiari malformation).
Conclusions: The most common diagnoses were DLBL and MALT lymphoma. 1 case was associated with prior chemotherapy and radiation suggesting a therapy-related pathogenesis. In 8 cases, pre-operative imaging was consistent with meningioma and the remaining case had imaging consistent with discitis. Follow up is available for 3 patients. 2 cases with DLBL are alive at 1.75 and 2 years with no recurrence. 1 case of MALT, which was status post renal transplant, is alive at 1 year with no recurrence. These data highlight that hematolymphoid lesions may arise primary to the meninges and often mimic meningioma by clinical and imaging studies.

1618 SOX2 Expression and EGFR Amplification Are Present in the Invasive Border of Glioblastoma and Could Be Used as Good Markers To Differentiate Tumor Cells from Reactive Glia.
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Background: We have previously shown that surgery done with 5-ala fluorescence allows highly precise separate sampling of the invasive border of the tumor in glioblastoma (GBM). In the border of GBM, the tumor cells have a mature aspect rather similar to reactive glia and discriminative markers between tumor cells and reactive glia are necessary. Sox2 is considered a marker of precursor cell and could be used as a good marker of tumor cells. By other way, EGFR amplification is a characteristic molecular alteration in GBM. However, it is not known how is the expression of these markers in the border of GBM and in the reactive glia.
Design: In 20 GBM the fluorescent quality of the tissue was used to take biopsies from the tumor center and the periphery. Only GBM with EGFR amplification were considered for this study. First, the EGFR amplification and the Sox2 and GFAP expression were evaluated by silver *in-situ* hybridization (SISH) and immunohistochemistry, respectively. These markers were compared between the center and the border of GBM. Second, these results were compared with the reactive glia in 19 cases of both vascular malformations and mesial temporal gliosis. As a control group, several representative samples of both center and border of GBM were cultured in a conventional medium and suspension cells were obtained and tested in a similar way. Non-parametrical statistical studies were applied.
Results: In 19/20 GBM, central tumor areas showed an intense nuclear staining in tumor cells against Sox2, but not in vessels or inflammatory cells. In the border of GBM, the expression of Sox2 was very similar, with no o scarce cytoplasmic expression. EGFR strong amplification similar to the center of the tumor was detected in every case in tumor cells from the periphery. The density of both amplified EGFR nuclei and Sox2 stained cells in the periphery correlated in most of cases (p<0,005). However, in the reactive glia, Sox2 was only cytoplasmic and less intense than in tumor cells and no EGFR amplification was detected at all. Interestingly, in the culture group, EGFR amplification was not detected and Sox2 was reduced, while the GFAP staining was preserved.
Conclusions: In the border of GBM, Sox2 expression and EGFR amplification are preserved and could be used as good markers to differentiate the peripheral tumor cells from the reactive glia.

1619 Phenotypic Variations in NF1-Associated Low Grade Gliomas: Possible Role for Increased mTOR Activation in a Subset.
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Background: Low grade gliomas are the predominant tumors arising in the central nervous system in neurofibromatosis type 1(NF1) patients. Although most of these represent pilocytic astrocytomas (PA) a subset are difficult to classify, and have

been termed "low grade astrocytoma subtype indeterminate" (LGSI). Some of these tumors have peculiar morphology, including plump cytoplasmic processes and macronucleoli.

Design: In the current study we performed electron microscopy, followed by gene expression, immunohistochemical and western blot analyses to identify biological differences underlying phenotypic variation in NF1-associated low grade glioma.

Results: Electron microscopy demonstrated glial intermediate filaments and frequent Rosenthal fiber material in both PA and LGSI. However, in addition dense core granules and/or aligned microtubules were found most frequently in the LGSI group only (2/3 cases), compared to the PA group (1/10 cases). Analysis of global gene expression data obtained using Affymetrix HG-U133 Plus2.0 chips (1 LGSI, 5 PA), and western blot analysis for pS6 (1 LGSI, 2 PA) demonstrated a gene expression profile reflecting neuronal differentiation and increased pS6 levels consistent with mTOR activation in the LGSI compared with PA. These findings were confirmed by immunohistochemistry for diagnostic neuronal markers, as well as combined pS6/pS6 kinase staining in 4/4 LGSI and 5/13 PA in formalin fixed paraffin embedded tissues (p=0.02).

Conclusions: Phenotypic variations in NF1-associated low grade glioma may be reflected in differential expression of neuronal-related genes and increased mTOR activation.

1620   O6-Methylguanine-DNA Methytransferase (MGMT) Immunohistochemistry as a Predictor of Resistance to Temozolomide in Primary CNS Lymphoma.

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Background: Primary central nervous system lymphoma (PCNSL) is an uncommon form of non-Hodgkin's lymphoma localized to the central nervous system(CNS). Therapy with methotrexate chemotherapy with or without radiation has a survival benefit for PCNSL patients, but these regimens carry a risk of significant toxicity, particularly for elderly patients or those with comorbidities. New therapies are needed for these patients and for recurrent disease after standard treatment. Temozolomide is an alkylating agent that exhibits good CNS penetration and is well-tolerated, with potential activity against PCNSL. Studies indicate that a major mechanism of resistance to alkylating chemotherapies such as temozolomide is the activity of O6-methylguanine-DNA methyltransferase (MGMT), an enzyme that repairs the DNA changes caused by these agents. Studies have demonstrated that increased levels of MGMT activity are associated with decreased responses to temozolomide in malignant glioma.

Design: A retrospective study of PCNSL patients seen at our center from 1990-2008 was conducted to assess the effect of treatment with temozolomide on immunocompetent patients with PCNSL. We studied the predictive value of MGMT analysis for treatment response to temozolomide.

Results: We identified 20 patients with PCNSL who were treated with temozolomide as a single agent. 6/20 patients demonstrated a response. MGMT expression levels were available for the five patients with complete response (CR), with a level of 20% for three of these patients, 25% for one patient, and 70% for the remaining patient. Two patients with CR were alive and had not experienced progressive disease at last contact, 6.7 and 8.5 years out from initiation of therapy. All non-responders for whom MGMT expression levels were available had an expression level of at least 30%, with 6/9 having MGMT expression levels of greater than 60%.

Conclusions: Our results indicate that temozolomide may be an effective therapy for PCNSL not amenable to standard therapies, and that high MGMT expression by immunohistochemistry can predict resistance to temozolomide. These data may guide future studies in therapy for this disease.

1621   Neural Stem Cells Deficient in BAX and BAK Manifest Profound Hyperplasia and Tumorigenesis.

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Background: BCL-2 family members are key regulators of the intrinsic pathway of programmed cell death or apoptosis. BAX and BAK are believed to have overlapping roles as the ultimate gatekeepers of mitochondrial apoptosis. Once activated, both proteins form homo-oligomers that induce permeabilization of the outer mitochondrial membrane, enabling released mitochondrial factors to activate caspases, which irreversibly execute the death program. Deletion of pro-apoptotic BAX and BAK from fibroblasts results in marked resistance to a variety of death stimuli. Double knock-out mice are predominantly non-viable and the survivors exhibit multiple developmental abnormalities, including excess neural stem cells in the periventricular region, hippocampus, cerebellum and olfactory bulb regions of the brain.

Design: To further explore the pathophysiology of Bax/Bak deletion in the adult central nervous system, we generated mice globally deficient in Bak with a conditional deletion of Bax in Nestin-positive cells.

Results: As anticipated, these mice develop proliferations of neural progenitor/stem cells within the subventricular zone (SVZ) niche, yet the degree of accumulation in adult brain is profound and includes a distinctive pattern of growth in rosettes. Furthermore, rare mice develop large brain masses, which in two cases were composed of benign-appearing, mature neurons, but in one animal appeared aggressive.

Conclusions: These studies underscore the importance of BAX and BAK in regulating Nestin-positive progenitor cell pools, with loss of function predisposing to both benign and malignant tumorigenesis.

1622   Applications of Optical Coherence Tomography (OCT) in Neuropathology.

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Background: Optical coherence tomography (OCT) is an imaging modality that has the potential for significant clinical impact in image-guided biopsy. The very high, near histological resolution (1-10 micron) and vascular imaging provided by OCT promises to improve the accuracy in the targeting of core biopsies. Only very limited investigations have been reported to date for applications in pathology, and none in neuropathology.

Design: In this study, we first sought to evaluate potential applications in the neurosurgical intraoperative consultation. Next, we investigated the effect of different fixatives on subsequent OCT imaging quality. Lastly, the ability of OCT to image brain autopsy material was assessed.

Results: For intraoperative frozen sections, we found that parameters such as cellularity and necrosis could be reliably detected, potentially improving tissue sampling in the future. Formalin fixation resulted in inferior resolution while fixation in an ethanol-based fixative preserved the OCT-visibility of many tissue structures. On unfixed brain autopsy tissue, OCT could reliably demonstrate blood vessels and even individual neurons.

Conclusions: OCT may represent a rapid way to extract information from tissue without requiring fixation, processing or sectioning. No tissue is permanently used up or altered in the process. In the future, OCT may have additional applications in pathology, such as in 3D reconstruction and tissue banking.

1623   IDH1 Mutation as a Predictor of Glioma Progression.

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Background: Adult low-grade gliomas have unpredictable progression rates. Molecular markers to augment prediction of progression are lacking. Mutations in IDH1, a key metabolic enzyme, have been in of secondary GBMs and predict a better prognosis. We asked whether mutation of IDH1 in LGG can predict time to progression to HGG.

Design: A TMA was created from cores of 75 grade II gliomas as well as 33 grade III gliomas. Adjacent cores were taken for high-throughput sequenome analysis of IDH1 and 2 mutations. The most common R132H-IDH1 mutation was also analyzed using a specific monoclonal antibody. P53 immunohistochemistry was oerformed as well.

Results: R132H-IDH1 mutations were detected by the mAb on the TMA in 52/75 of all grade II gliomas as well as in 26/33 grade III gliomas. In addition to detecting the majority of tumors with R132H IDH1 mutations which had been identified by immunohistochemistry on the TMA, sequencing revealed mutations in IDH2 in 1 OII (R172K), 2 AAIII (R172K, R172G), and in 1 AOAIII (R172G). IDH1 and IDH2 mutations were strongly associated with a longer PFS both in grade II and especially in grade III gliomas. This strong association also held true with respect to the OS. p53 i\reactivity did not show any association with PFS or OS and was independent of IDH1/IDH2 mutation status.

Conclusions: We confirmed the high frequency of R132H mutations in gliomas of different grades and the almost complete absence of IDH2 mutations. The correlation between sequencing and immunohistochemistry for the R132H-IDH1 mutation is very high. Antibody staining was more sensitive than sequencing especially in grade II gliomas. This observation is not surprising due to the heterozygous nature of the mutation and the highly infiltrative growth pattern of most gliomas. However, 4 patients whose tumors harbored R172-IDH2 mutations also did significantly better with respect to PFS and OS. In summary IDH1/IDH2 mutation status is a significant predictor both for PFS as well as for OS.

1624   Challenges in the Differential Diagnosis and Subtyping of Primary Central Nervous System Lymphomas.

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Background: In surgical neuropathology, the challenges in the diagnosis of primary central nervous system lymphoma (PCNSL) include defining prognostic markers and the difficulties in being able to exclude a systemic lymphoma. Recent studies identified two general subtypes of diffuse large B-cell lymphoma (DLBCL) with different prognostic features based on MUM-1, BCL6 and CD10 expression. The utility of this subtyping in the CNS is not entirely clear.

Design: In order to determine the challenges in the diagnosis and prognostication of PCNLS, we reviewed the Department of Pathology archives over the last 20 years. Cases without sufficient information or pathological material were excluded. Clinicopathological and immunohistochemical features of were correlated with outcome parameters.

Results: Among 136 cases diagnosed as PCNSL during the last 20 years, we included 97 patients into the study. Sixteen patients (17%) were subsequently proven to have systemic lymphoma. Among the remaining 81 patients, 58 (32 male 26 female) had no evidence of immunosuppression. The median age of this group was 63 and all tumors were in the cerebral hemispheres except for 3 in the cerebellum and one in the midbrain. In 18 patients (15 males, 3 females), HIV/AIDS was established both clinically and serologically. In this group, the median age was 38 and only two tumors were outside the cerebral hemispheres. In addition, 5 patients fulfilled the criteria for monomorphic B-cell PTLD. The diagnosis could be established only after immunohistochemical stains in 38 of the 97 patients. The primary suspicion was demyelinating disease in 6 cases

and a poorly differentiated malignancy (undifferentiated carcinoma, glioblastoma or melanoma) in 36 cases. Markers utilized in this study were not helpful to distinguish a systemic DLBCL from PCNSL.

Conclusions: Most pertinent diagnostic challenges in PCNSL include "treated" lymphoma versus demyelinating disease and other malignant small blue round cell tumors. Work-up of PCNSL should include exclusion of a systemic disease, especially in older individuals without HIV/AIDS. Our results also support the conclusion of recent reports on the phenotypic aspects of PCNLS and question the utility of the recent DLBCL subtyping in the CNS.

1625 Luminal A Subtype Predicts Improved Survival in Patients with Metastatic Breast Carcinoma to the Brain.

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Background: The most common central nervous system (CNS) neoplasm is metastasis from another site, with breast being the second most common primary. Breast cancer patients typically have advanced systemic disease by the time CNS involvement is manifested. Patients with triple negative primary breast cancer and those with Her2 amplification usually are at an increased risk for metastasis. However, very little is known about how to predict prognosis after the patients develop brain metastases. Currently, therapeutic options are limited with surgery generally only offered to those with solitary lesions, and prognosis is poor. We proposed that the molecular subgroup to which the breast cancer belongs, may influence the time from brain metastasis to death.

Design: We identified 59 cases of metastatic breast cancer to the CNS. Cases were evaluated for various demographic, clinical and pathologic parameters. In addition, immunohistochemistry for ER, PR, Her2, EGFR, and Ki67, and Her2 FISH analysis were performed. Tumors were divided into one of four established molecular subgroups based on ER, PR, and Her2 status—basal, intrinsic Her2, luminal A, and luminal B. Overall survival from the time of metastasis was plotted for each of the four groups using a Kaplan-Meier curve.

Results: Median overall survival for basal, intrinsic Her2, luminal A and luminal B subtypes was 9.3, 9.3, 43.7 and 17.4 months, respectively. Median overall survival for all groups combined was 16.7 months. Chi-square pairwise comparisons showed a significant difference in overall survival between the basal and luminal A subtypes ($p<0.001$). While there was a trend showing that luminal A cancers also do better than the intrinsic Her2 and luminal B subgroups, the difference did not reach statistical significance.

Conclusions: Patients with luminal A type breast cancers had a statistically significant increased overall survival from time of metastasis when compared to those of the basal subtype. The ability to stratify patients into prognostically significant categories is vital to tailoring treatment regimens to individual patients.

1626 Expression of EGFRvIII in Glioblastoma: Prognostic Significance Revisited.

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Background: *In vitro* and *in vivo* studies have shown that expression of the epidermal growth factor receptor variant III (EGFRvIII) is associated with increased proliferation and aggressiveness of glioma cells. However, the impact of EGFRvIII on survival of patients with glioblastoma (GBM) has not definitively been established.

Design: We prospectively evaluated 73 adult patients with primary GBM who underwent surgical resection followed by standard radiotherapy and temozolomide. Clinical variables included age, sex, Karnofsky Performance Status (KPS), Radiation Therapy Oncology Group RPA score, and extent of tumor resection. Tumor samples were analyzed for expression of EGFRvIII and MGMT promoter methylation by RT-PCR, and for expression of PTEN by immunohistochemistry. Overall survival (OS) curves were estimated by the Kaplan-Meier method. Multivariate analysis was performed by Cox regression model. In 10 patients who presented with tumor recurrence, EGFRvIII was determined both before and after radio-chemotherapy by Real Time RT-PCR. Sensitivity to temozolomide was assessed in EGFRvIII-positive and EGFRvIII-negative GBM cell lines established from the same tumor.

Results: Age$\leq$60 years, preoperative KPS>70, RPA score III and IV, and Ki67 index<20% significantly associated with longer OS (p=0.0069, p=0.0035, p<0.0001, and p=0.0286, respectively). EGFRvIII expression did identify patients with significantly longer OS (p=0.0047). Patients with EGFRvIII expression and normal PTEN showed better OS relative to those cases with EGFRvIII expression and loss of PTEN (p=0.0054; 0.0028). On multivariate analysis, age>60 years (p=0.0089), KPS$\geq$70 (p=0.0078), Ki67 index$\leq$20% (p=0.0069), and expression of EGFRvIII (p=0.0255) were independent prognosticators for OS. In GBMs recurring after radio-chemotherapy, EGFRvIII was reduced by 4.5 fold in average as compared with the paired tumors at primary surgery. *In vitro*, the EGFRvIII-negative cells were more resistant to high doses of temozolomide than the EGFRvIII-positive ones.

Conclusions: EGFRvIII expression is associated with prolonged survival of GBM patients treated with surgery and adjuvant radiotherapy and temozolomide. Depletion of EGFRvIII in recurrent GBMs and low sensitivity to temozolomide *in vitro* indicate that the EGFRvIII-negative cell fraction is involved in resistance to radio-chemotherapy and tumor repopulation.

1627 Spinal Cord Ependymomas: UCSF Experience 1983-2010.

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Background: The ependymal tumors in the spinal cord are graded in a similar fashion as the intracranial examples and are designated as grades I through III based on the WHO criteria. Subependymomas and myxopapillary ependymomas are WHO grade I tumors, while classical ependymomas are can be grade II or III. Most spinal ependymomas have a more favorable outcome but many studies combine cranial and spinal cord examples without regard to their different biological behavior.

Design: In order to determine the types and behavior of spinal cord ependymomas, we reviewed the Department of Pathology archives during a 27-year period (1983-2010). Patients without available pathology material or sufficient information were excluded. Histopathological features of tumors were recorded and were correlated with tumor clinical findings in order to determine their association with outcome parameters.

Results: Among a total of 352 patients with primary spinal cord neoplasms, 134 (38%) had ependymomas (85 male/49 female). Thirty patients had WHO grade I ependymomas (28 myxopapillary, 2 subependymomas; median age: 28.2), 101 had WHO grade II (89% classic type, 5% focal myxoid, 6% tanycytic; median age: 43.3), and three had WHO grade III tumors. Myxopapillary ependymomas were located predominantly in the lumbar spine, while grade II ependymomas were more common in cervical cord. Uncommon findings in ependymomas included necrosis (17% grade I, 19% grade II, 100% grade III), degenerative changes, pseudoglandular formation and extensive collagenization (25% grade I, 24% gradeII). Gross total resection (GTR) was achieved in 57% of grade I ependymomas, 58% grade II ependymomas and one of three grade III ependymomas. All three grade III ependymomas recurred and underwent additional surgery, chemotherapy and/or radiation. The recurrence rate was 32% in grade I and 19% in grade II ependymomas. Up to 20% of grade I and only 9% of grade II ependymomas required additional surgical intervention. Progression free survival time was 74 months in grade I, and 164.6 months in grade II ependymomas (p=0.07). Progression free survival time in grade II ependymomas was dependent on the extent of the surgery (p=0.01).

Conclusions: Despite their classification as grade I tumors, spinal cord myxopapillary ependymomas appear to have similar if not worse behavior as that of grade II spinal cord ependymomas, with increased recurrence rate, shorter progression free survival, and higher likelihood of subsequent surgical interventions.

1628 Uncommon Patterns and Clinical Features of Peripheral Nerve Sheath Tumors of the Spinal Cord: UCSF Experience 1983-2010.

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Background: Peripheral nerve sheath tumors (PNSTs) are one of the most common primary neoplasms in the spinal cord and the overwhelming majority is benign. While complete resection is the goal, incomplete resection may be required to preserve function. The challenges in the management of the PNSTs are often related to their long natural history and the unusual patterns that do not exactly fit the prototypes. Such unusual patterns may often cause uncertainty about the diagnosis.

Design: In order to determine the frequency and relevance of uncommon patterns seen in spinal cord PNSTs, we reviewed the Department of Pathology archives during a 27-year period (1983-2010). Patients without available pathology material or sufficient information were excluded. Histopathological features of tumors were recorded and were correlated with tumor clinical findings in order to determine their association with outcome parameters.

Results: Among a total of 352 patients with primary spinal cord neoplasms, 178 (51%) had PNSTs (109 male/69 female; median age: 47.7; range: 1-89). There were 140 schwannomas (87% classic type, 6% myxoid, 4% cellular, 2% hyalinizing, and 1% melanotic), and 38 neurofibromas (26 patients with NF1 and 1 with NF2). Trapped ganglion cells were seen in 56% of neurofibromas and only 2% of schwannomas. Degenerative changes and pleomorphic nuclei were present in 14% and 24% of schwannomas, respectively. Uncommon findings in schwannomas included necrosis (4% of cases), pseudoglandular formation (3%), epithelioid differentiation (2%), and focal infiltrative pattern (1%). Chronic inflammatory infiltrates other than macrophages were seen in 20% of schwannomas and only 4% of neurofibromas. There was no significant correlation between recurrence and extent of resection (p=0.2519) or location (p=0.0529) in schwannomas. Aggressive clinical course was seen in 2 of 5 cellular and both melanotic schwannomas. Myxoid and hyalinized types had a significantly more indolent course.

Conclusions: Necrosis, trapped ganglion cells and epithelioid features are rare features that may cause challenges in the diagnosis but do not seem to influence biological behavior. Cellular and melanotic Schwannomas are among those with more aggressive course. Extensively hyalinized or myxoid Schwannomas have excellent prognoses even in the face of subtotal resection. Some subtotally resected Schwannomas may not require additional treatment.

1629 Absence of IDH1 R132H Mutation Predicts Rapid Progression of Non-Enhancing Diffuse Glioma in Older Adults.

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Background: Advanced age and the presence of contrast enhancement are regarded as poor prognostic factors in diffuse glioma. It is recognized that some diffuse gliomas can present initially as non-enhancing tumors and rapidly progress to a pattern of ring-enhancement, characteristic of glioblastoma (GBM) over a period of weeks to a few months. Mutations involving *IDH1* (isocitrate dehydrogenase 1) have recently emerged

as an important diagnostic, predictive and prognostic marker in glioma. R132H is the most common mutation, expressed in over 80% of WHO II and III diffuse gliomas and secondary GBM, but in less than 10% of primary GBM. In this study we correlate IDH1 R132H expression of non-enhancing gliomas in older adults with prognosis.

Design: Five patients with ages above 50 years and non-enhancing diffuse glioma were identified. Gliomas were classified according to the WHO 2007 grade, and 1p/19q deletion status when available. Representative sections were stained with an antibody specific for mutated *IDH1* (anti-IDH1 R132H). Glioma outcome was correlated with IDH1 R132H status.

Results: Two groups of patients were identified. A favorable prognosis group included three patients, ages 51, 59 and 51 who presented with non-enhancing diffuse glioma, WHO grades III; II, 1p intact /19q deleted; and II, 1p/19q intact, respectively. All three tumors showed intense cytoplasmic and weaker nuclear IDH1 R132H staining. All three patients were alive and recurrence-free at the last contact with follow-up periods between 4 months and 3.8 years. A poor outcome group comprised two patients presenting with non-enhancing diffuse glioma WHO grades III and II at ages 51 and 55, respectively. The tumors rapidly progressed after 2 and 4 months, respectively, to ring-enhancing lesions that were subsequently diagnosed on surgical resection as GBM, WHO IV. This group showed absent IDH1 R132H expression, which is characteristic of primary GBM.

Conclusions: Our study indicates that negative IDH1 R132H mutation status in non-enhancing diffuse glioma of older adults is a negative predictive factor associated with rapid progression to a higher grade, ring-enhancing GBM. The associated shorter interval of progression and negative IDH1 R132H mutation status suggests a similar de novo pathogenetic mechanism as in primary GBM.

1630   PIT-1, and ERα Transcription Factors, and PTTG-1 Gene Expression in Pituitary Adenomas.
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Background: Pituitary adenomas (ADHs) are diagnosed as benign tumors even though they can be aggressive. In the pituitary development transcriptions factors play an important role in determining cell phenotypes and proliferation. Overexpression of transcription factors has been detected in ADHs suggesting their role in the formation of pituitary tumors. Objective: The aim was to evaluate the secretory activity, transcription factors expression and proliferative markers in ADHs.

Design: In 99 pituitary adenomas immunohistochemistry against PCNA, Ki-67 antigen, Pit-1, ERα, and pituitary hormones (prolactin, growth hormone, FSH, LH, TSH, ACTH) was made. Correlation analysis among hormonal activity, cellular proliferation, and transcription factors expression was done.

Results: ERα expression correlate with GH, ACTH hormones, and plurihormonal adenomas (p=0.047, p=0.008, p=0.042 respectively); Pit-1 had correlation with prolactin hormone and non-secretor ADHs; high Ki-67 expression correlate with Pit-1 (p= 0.019) and ERα (p= 0.017), and PCNA correlate with Pit-1 (r²=0.145, p=0.001), and was high in secretor than in non-secretor ADHs (p=0.034). PTTG-1 shows correlation with plurihormonal tumors in general (p=0.014), with FSH and TSH in particular (p= 0.056; p=0.053), and with non-secretor (p=0.040). Also PTTG-1 expression is associated with ERα expression (p=0.000) and PCNA expression (p=0.028).

Conclusions: Pit-1 and ERα are involved in proliferation inducing the cyclin D1 expression; Pit-1 over expression has been founded in GH, Prl and TSH adenomas. Is strongest predictor of prolactinoma development, ERα and Pit-1 transcription factors expression shows that it can be useful to distinguish the hormonal activity of the ADHs overall in plurihormonal ones in which its diagnostic is difficult, and its correlation with the proliferative markers could help to give an idea of their biological behaviour.

1631   Isocitrate Dehydrogenase 1 *(IDH1)* R132H Mutation Is Not Detected in Angiocentric Glioma.
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Background: Mutations of isocitrate dehydrogenase-1 gene (*IDH1)*, most commonly replacement of arginine at position 132 by histidine (R132H) have been described in WHO grade II and III diffuse gliomas and secondary glioblastoma, but are rare in primary glioblastoma and other solid tumors. Immunohistochemistry (IHC) utilizing a mouse monoclonal antibody has a high specificity and sensitivity for detecting IDH1 R132H mutant protein in sections from formalin fixed paraffin embedded (FFPE) tissue.

Angiocentric glioma (AG) is a unique neoplasm with mixed features of diffuse gliomas and ependymal differentiation, recently included as a grade I neoplasm in the 2007 WHO classification of CNS tumors. This study was designed to evaluate the presence of the *IDH1* R132H in AG.

Design: Three cases of AG were collected and the diagnoses were confirmed. Expression of mutant IDH1 R132H protein was determined by IHC on representative FFPE sections using the anti-Human mouse monoclonal antibody IDH1 R132H (Dianova, Hamburg, Germany). Known cases of grade II-III glioma, confirmed by PCR sequencing, were stained to confirm that mutant IDH1 protein was detected under similar staining conditions.

Results: All three cases were males, 3, 5 and 15 years old, with intra-axial tumors in the right posterior parietal-occipital, right frontal and left frontal lobes, respectively. All three cases showed characteristic morphology of AG, including a monomorphous population of bipolar, slender cells, radially and longitudinally ensheathing cortical

blood vessels, as well as diffusely infiltrating parenchyma. All three cases were negative for the presence of IDH1 R132H mutant protein (0/3). All controls showed positive staining of the mutant-specific antibody in grade II-III diffuse gliomas.

Conclusions: *IDH1* R132H mutation has been described as a common molecular signature in grade II and III diffuse gliomas, and secondary glioblastomas; however, AG has not been evaluated. The absence of mutant IDH1 R132H protein expression in AG further distinguishes this unique neoplasm from diffuse gliomas.

1632   Concordance Rates of O(6)-Methylguanine DNA-Methyltransferase Promoter Methylation in Primary-Recurrent Paired Glioblastoma Samples.
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Background: O(6) methylguanine DNA-methyltransferase (MGMT) is a mechanism of resistance for glioblastoma cells against alkylating and methylating chemotherapeutic agents. Glioblastomas lacking MGMT expression are more sensitive to these agents. The MGMT promoter methylation at CpG islands leads to MGMT silencing, and can be detected as a potential predictive test. Changes in MGMT methylation status during radiation and chemotherapy might influence response to therapy.

Design: Patients with glioblastoma who had undergone radiation and chemotherapy, and were subsequently diagnosed with residual/ recurrent disease were identified. Representative formalin-fixed paraffin-embedded (FFPE) tissue blocks were selected from the initial and subsequent surgical specimens. MGMT methylation status was determined by methylation-specific PCR (MSP), performed in triplicate, while blinded as to any clinical data.

Results: There were 7 males and 2 females, 34 to 66 years old (mean 52 yrs) At initial diagnosis. All underwent surgical resection, radiation therapy of up to 60 Gy, and chemotherapy with temozolomide. Residual/ recurrent disease was diagnosed at 2 to 45 months (mean 19.6 months) from initial diagnosis. Seven patients survived 9 to 46 months (mean 23.8 months) to last contact, while 2 died of glioblastoma, confirmed on autopsy.

Seven cases retained MGMT-promoter methylation status in initial and subsequent specimens, as methylated (MGMT-M) in 2/9 (22%) and unmethylated (MGMT-U) in 5/9 (56%). One case initial MGMT-M and subsequent MGMT-U. A second case had initial MGMT-U and subsequent MGMT-M. These two cases were 34 and 36 years old (compared to 57 years in retained status), recurred at 17 and 18 months (compared to 20 months in retained status), and survived 17 and 18 months from initial diagnosis (compared to 25.5 months in retained status), with one dying of disease and one alive with disease at last contact. In this study, we did not find any significant association between initial and subsequent MGMT-promoter methylation status.

Conclusions: While majority of glioblastomas appear to retain their MGMT- promoter methylation status even after radiation and chemotherapy, these data suggest that the methylation status can change in a small proportion of glioblastomas. It has been reported that MSP in FFPE tissue may lack of reproducibility in a proportion of samples. It is possible that technical issues are responsible for our discordant cases. Further work is required to examine this more fully.

1633   TMA Analysis of Invasive and Non-Invasive Meningiomas.
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Background: The pathogenesis of meningioma bone invasion remains unknown. Osteopontin, matrix metalloproteinase's (MMPs), and integrins (ITG) have been found to play a role in bone infiltration in solid tumors including breast and prostate carcinomas. We investigated immuno expression of these proteins in bone invasive and non-invasive meningiomas using the high throughput tissue microarray (TMA) method.

Design: Clinical and Pathologic data was collected on 57 patients with invasive (IM) and non-invasive (NIM) meningiomas. TMA was generated and immunohistochemical analysis for osteoponin, integrin-beta-1 (ITG-b1) and matrix metalloproteinase-2 (MMP-2) performed. Microscopic evaluation of included scoring immunostaining intensity and percentage in tumor and vascular endothelial cells.

Results: MMP-2, OPN, and ITG-b1 immunoreactivity was cytoplasmic and/or membranous, with ITG-b1 being predominantly membranous in endothelial vessel and tumor cells, and OPN being mostly membranous in endothelial cells.**ITG-b1:** ITG-b1 expression exhibited a striking concentric perivascular pattern in some meningiomas. Tumor cell immunoreactivity was significantly higher in invasive transbasal meningiomas than NIM ones (p = 0.0356). There was a correlation between ITG-b1 and OPN immunoexpression (R=0.4, p=0.03). **OPN:** Immunoexpression was significantly higher in invasive transbasal meningiomas compared to NIM meningiomas (p = 0.05).**MMP-2**: Non-invasive transbasal meningiomas exhibited higher MMP-1 immunoexpression in vascular endothelial cells compared to invasive meningiomas (p = 0.0079).

Conclusions: We have demonstrated key differentially expressed proteins between IM and NIM that may lead to greater understanding of the biological substrate for invasive behavior in these tumors.

1634   Genetic Alteration of Pediatric Glioblastomas.
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Background: Pediatric high grade glioma (HGG) is a relatively under-studied tumor of the central nervous system. They are highly invasive tumors with poor response to conventional treatment. Although they are morphologically similar to HGGs of other age groups, some authors insisted that the WHO classification system may not be accurately

representative of the histopathological diversity of the childhood brain tumors. Unlike those in adults, the tumorigenesis of HGG in children remained poorly understood partly due to the limited availability of suitable models or cell lines.

Design: Twenty five cases of non-brainstem primary GBMs obtained from two hospitals namely, Seoul National University Hospital and Yonsei University Hospital from 1989 to 2009 were used. Gene expression profiling studies was done using Illumina Human HT-12 v3 gene Expression Bead Chip (Illumina, Inc., San Diego, CA) that contained 48,804 developmental and cancer genes. Materials were mRNA extracted from 4 childhood and 6 adults GBMs and one case of nonneoplastic child brain, which were fresh frozen tissue.

Results: Of the 25 cases, p53 overexpression was found in 25.9% and loss of p16 and PTEN expression were noted in 61.5% and 25.9%, respectively. Immunohistochemistry with EGFR and EGFRvIII (Zymed) revealed overexpression of the proteins in 40% and 61.5%, respectively but EGFR gene amplification and high polysomy by fluorescence-in-situ hybridization were only observed in 25.9%. 1p and 19q deletion was present in 8% and 4%, respectively. CD133 was positive in 32 %. Using non hierarchical clustering analysis, we found that two pediatric GBMs from younger age group (8 and 9 years old) possessed different genetic profile compared to two others that belonged to a relatively older age groups (11 and 13 years old) and the adult GBMs. In the cases from the younger age group, we identified 24 up-regulated and 40 down-regulated genes. The most significantly up-regulated genes among these were TNFRSF14, ELF4, and some mRNA of RRAD. The genes that were down regulated were Cyclin D2, Neurocan, phosphodiesterase 4B, OLIG1, etc.

Conclusions: In conclusion, the EGFRvIII overexpression and p16 loss were more frequent findings in pediatric GBMs than in adult GBMs. However, in other parameter such as p53, EGFR overexpression and PTEN loss were just comparable between the two groups of neoplasms. Pediatric GBMs in children less than 10 years old have different gene expression profile from those in the older child and adult GBMs suggesting that different molecular pathways may exist in this group of neoplasm.

1635 Vascular Endothelial Growth Factor Receptor-2 and Vascular Endothelial Growth Factor-A Are Localized Primarily to the Vasculature in Pilomyxoid Astrocytoma: A Comparative Study with Juvenile Pilocytic Astrocytoma.
SG Sharma, AG Saad. Arkansas Children's Hospital, Little Rock.

Background: In recent WHO classification, pilomyxoid astrocytoma (PMA) has been added into the category of histological variants of pilocytic astrocytoma (PA). While PMA often show focal features of PA, it has a more aggressive clinical course. Vascular endothelial growth factor (VEGF) signaling is key to physiologic and pathologic angiogenesis and lymphangiogenesis, and is an established target in the development of anticancer therapeutics. VEGF-A is an important driver of the neovascular growth required to support solid tumor progression. The primary signaling receptor for VEGF-A is VEGFR-2, and activation of VEGFR-2 by VEGF-A directs the migration and extension of sprouting vessels.

Design: Six PMAs and 15 PAs are included in this study. Five cases of PMAs were identified by reviewing all cases of PAs on files in the Department of Pathology at Arkansas Children's Hospital since 1970. PAs cases consisted of the last 15 cases accessed in our files. In each case, three 4-μm-thick sections were performed and immunostained with antibody against VEGFR-2, and VEGF-A. The results are correlated with clinical prognosis.

Results: PMAs cases consisted of 4 males and 2 females (median age 3.5 years). PAs cases consisted of 9 males and 7 females (median age 7.9 years). Patients were followed up for a median time of 5.75 years (range 1.15-16.56 years) after the first diagnosis. Median disease-free interval was 2.3 years in patients with PMAs and 7.7 years in PA. Recurrence occured in 4 patients with PMAs and in 2 patients with PA. VEGFR-2 were expressed on vascular endothelium but not on malignant cells in six PMAs and focally on endothelial cells and malignant cells in two PMAs. There was a strong correlation between the expression of VEGFR-2 (P=0.009) and VEGF-A (P=0.01) on vascular endothelium and shorter disease-free survival rate. When VEGFR-2 and VEGF-A were expressed on endothelial and tumor cells, the disease-free survival rate decreased significantly (P=0.0008). No expression of VEGFR-2 or VEGF-A was observed in patients with PA including the case with recurrence. months after surgery. No statistical correlation was attempted (only one case).

Conclusions: We demonstrate for the first time the preferential expression of VEGFR-2, and VEGF-A in intratumoral vasculature and focally on tumor cells in patients with PMAs. The expression of VEGF may account for the high rate of recurrence in patients with PMAs. Furthermore, patients with PMAs may benefit from anti-VEGF targeted therapy.

1636 Inhibition of Signal Transducer and Activator of Transcription 3 (STAT3) by the Multi-Kinase Inhibitor Sorafenib Overcomes TRAIL-Resistance in Malignant Glioma Cells.
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Background: Glioblastoma (GBM) is the most common primary malignant brain tumor with a dismal prognosis. Therefore, new therapeutic strategies are highly warranted. Tumour necrosis factor-related apoptosis-inducing ligand (TRAIL) is a promising anti-cancer reagent that induces apoptosis specifically in cancer cells. However, many tumor cells, including GBM cells, are primary resistant to its pro-apoptotic effects. Sorafenib is an oral kinase inhibitor that has been shown to cross the blood-brain barrier and to inhibit tumor growth in vitro and in vivo by interfering with STAT3-signalling, being constitutively active in GBM. In this study, we analyzed whether sorafenib can overcome TRAIL-resistance in glioblastoma cells and the underlying molecular mechanisms.

Design: Glioma cell lines were treated with sorafenib, TRAIL or the combination of both. Cell viability was assessed by MTT-Assay. Apoptosis and caspase-activity were analysed by Annexin V/PI staining and immunoblotting. Analysis of anti-apoptotic proteins was assessed by immunoblotting. Expression levels of STAT3 were modulated by siRNA or plasmid-based over-expression of constitutively active STAT3.

Results: Single treatment with either suboptimal amounts of sorafenib or TRAIL did not result in efficient induction of apoptosis (programmed cell death). However, the combination treatment consisting of clinically achievable suboptimal doses of sorafenib and TRAIL led to rapid apoptosis in glioma cells. The combination treatment of sorafenib and TRAIL significantly activated both the initiator-caspases-8/-9 and effector-caspases-3/-7. Mechanistically, sorafenib inhibited signal transducers and activators of transcription 3 (STAT3) phosphorylation (Tyr 705) known to be constitutively active in both glioblastoma specimens and cell lines. Forced expression of constitutively active STAT3 (STAT3-CA) attenuated TRAIL-sorafenib mediated apoptosis. Conversely, acute ablation of STAT3 by siRNA sensitized glioma cells to TRAIL mediated cell death.

Conclusions: Targeting STAT3 by sorafenib in GBMs might be a powerful tool to overcome the highly apoptotic resistant phenotype of gliomas and to sensitize them to the proapoptotic effects of TRAIL.

1637 Choroid Plexus Carcinoma in Adults: Clinicopathologic, Immunohistochemical, and Imaging Studies of Cases Presenting at Unusual Sites.
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Background: Although choroid plexus carcinoma is considered more common in pediatric populations, <20 cases have been reported in adults, including, rarely, within the extraventricular brain parenchyma.

Design: Consult files of the University of Michigan and Medical University of South Carolina were reviewed.

Results: Three cases were identified; gender/ages F/67, M/44, and M/60. Presenting symptoms included headache, hearing loss, and memory loss with dysnomia, respectively. Imaging identified sites as left lateral temporal; right cerebellopontine angle, as right anterior temporal. Imaging interpretation of the first was primary glioma versus metastatic carcinoma; the second, acoustic schwannoma versus meningioma, and third, again, glioma versus metastasis. Two of the three cases (F/67 and M/44) showed a clear transition from normal choroid plexus to atypical, malignant cells including solid areas with increased nuclear hyperchromasia and mitoses consistent with frank carcinoma. The third case showed a highly anaplastic morphology with sheets of pleomorphic cells, apoptosis and necrosis reminiscent of glioblastoma. However, multiple foci demonstrated differentiation into papillae with thin-walled vessels surrounded by hobnailed cells, suggesting choroid plexus histogenesis. In the F/67 and M/60 cases, GFAP and S100 stained negative or only focally, both were positive in the third M/44. Prealbumin/transthyretin was positive, supporting choroid plexus origin in the two more poorly differentiated cases (M/60 and F/67), including in the more anaplastic component. In the M/60 and M/44 cases, synaptophysin was positive, and MIB-1 proliferative index 90% and 13%, respectively. In the M/60 and M/44 cases, both CK7 and CK20 were weak to negative, while in the F/67 and M/44 cases CEA staining was negative and positive, respectively.

Conclusions: Choroid plexus carcinoma presents rarely in adulthood and may occur at sites mimicking more common malignancies. Two of three cases showed a transition from identified choroid plexus tissue, the third evinced a markedly dedifferentiated morphology with only focal papillation. in such cases we still observed clear positivity with prealbumin/transthyretin, supporting the utility of this marker in identification of tissue of origin.

1638 Unusual Histological Findings in a Cohort of Gliomas with High Grade Features: A Clinicopathological Study of 5 Cases at a Single Institution.
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Background: Rosenthal fibers (RF) and eosinophilic granular bodies (EGB) are commonly encountered in pilocytic astrocytoma (PA), pleomorphic xanthoastrocytoma (PXA) and ganglioglioma, and usually associated with long standing processes. There is limited literature addressing the clinical significance of RF and EGB in gliomas with high grade features (HGF). The aim of this study is to evaluate the clinical, radiologic and pathologic findings in such cases.

Design: The pathology database for the time period 2003-2010 was queried for Gliomas with HGF and there were 5 cases in which RF and/ or EGB were described as a prominent finding. The pathologic diagnoses were: 2 PXA, 2 grade III gliomas, and 1 mixed tumor with glial and neurocytic features. The clinical follow-up ranged from 1 month to over 20 years (see Table 1).

Results: All patients underwent tumor resection. Histologically, all tumors showed high grade features including high cellularity, pseudopalisading necrosis, vascular proliferation and variable mitotic activity. Two cases (#1 and #2) had EGB and RF. Two (#3 and #5) had RF and one (#4) had EGB.

Table 1. Summary of cases of glioma with HGF and RF/EGB

Case	Diagnosis	Grade	Age/Sex	Presentation	Imaging	Follow-up
1	PXA	II-III	16M	Acute; 1 week	Left frontal lobe enhancing mass	9mo; stable
2	Mixed tumor with glial and neurocytic features	Uncertain	61F	Increasing headache 1 month	4th ventricle complex cystic mass with peripheral enhancement	1 mo; stable

3	Glioma with pilocytic features	III	33F	Recent headache, seizure	Right frontal lobe mass with decreased attenuation	13 mo; stable
4*	PXA*	II-III*	31M*	Headache *	Right frontal lobe enhancing mass *	14 years; alive *
5	Astrocytoma	III-IV	29M	Mental status changes	Left frontal lobe mass	6 years; recent status unknown

* indicates patient's age, presentation and follow-up from the 1st recurrence as grade III glioma (9 years after initial diagnosis of PA); mo: month

Conclusions: This study is a collection of gliomas with HGF showing the somewhat rare finding of numerous RF and EGB. While it is difficult to draw definitive conclusions from this small patient sample, 4 of the 5 patients were less than 35 years of age at diagnosis. This is at least 10 years younger than the mean for high grade gliomas. Additionally, most patients had stable follow-up, with the longest being more than 14 years after initial diagnosis. Such gliomas with HGF and RF/EGB could be a unique set of tumors that present acutely yet behave more indolently compared to the usual high grade gliomas.

1639 Osteopontin Immunoexpression in Primary Central Nervous System Lymphoma, and Comparison with Nodal and Extranodal Diffuse Large B-Cell Lymphoma.
J Yuan, K Gu, S Sharma. Medical College of Georgia, Augusta; University Hospital, Augusta, GA.
Background: Primary central nervous system lymphoma (PCNSL) is an aggressive diffuse large B-cell lymphoma (DLBCL) mostly of activated B cell type (ABC), with poor prognosis, yet confined to the CNS microenvironment. Osteopontin, a cell-matrix glycoprotein, is associated with progression, metastatic spread and poor prognosis in several tumors. Osteopontin was the most up-regulated gene in PCNSL compared to nodal and extra-nodal DLBCL (N-DLBCL, EN-DLBCL) in recent cDNA microarray studies. We aimed to validate the protein expression of osteopontin and assess its prognostic value in PCNSL.
Design: We retrieved 19 archival cases of PCNSL, 11 N-DLBCL, and 17 EN-DLBCL from pathology records. Immunohistochemical (IHC) staining was performed for osteopontin and Ki67 on formalin-fixed paraffin-embedded sections using Envision Plus System. Staining for osteopontin was semi-quantitatively stratified and scored both by percentage positivity of tumor cells (0%, 1-25%= score 1, 26-50%=2, 51-75%=3, and 76-100%=4) and staining intensity (none=0, weak=1; moderate=2; intense=3), and an overall score (0 to 12) calculated for each case by multiplying percentage score with intensity score. This data was correlated with Ki67 proliferative indices.
Results: Osteopontin nuclear immune-expression was observed in 18 of 19 (95%) PCNSL cases, 16 of 17 (95 %) EN-DLBCL, and 3 of 12 (25%) N-DLBCL cases. Staining intensity was moderate to strong in most PCNSL cases (especially intense in perivascular and infiltrating neoplastic cells), but weaker and noted in fewer cases sequentially in the EN- or N-DLBCL groups. The overall immunostaining scores were significantly higher in PCNSL group (6.4 ± 3.6) and in EN- (4.4 ± 4.1) than N-DLBCL (0.3 ± 0.7) groups (p< 0.001). The difference in osteopontin IHC scores between PCNSL and EN-DLBCL group, was however not statistically significant (p=0.09). Further, high osteopontin expression was not associated with high Ki67 proliferation index.
Conclusions: Osteopontin immunoexpression was highest in PCNSL, especially in perivascular and infiltrating neoplastic cells, sequentially followed by EN-DLBCL and N-DLBCL. No association was observed between osteopontin expression levels with proliferative index. Future studies are required to assess the prognostic/predictive role of osteopontin in PCNSL.

1640 Are There Any Differences in the Expression of IDH1 and P53 Proteins between Astrocytoma and Oligodendroglioma?
M Zheng, S Sharma. Medical College of Georgia, Augusta.
Background: Isocitrate dehydrogenase 1 (IDH1) mutation has been well-described in diffuse glioma in recent large studies, with a reportedly similar frequency in astrocytomas and oligodendrogliomas. We compared the expression of IDH1 and p53 in diffuse gliomas to assess any differences between astrocytoma and oligodendroglioma of different grades.
Design: A total of 27 glioma cases were studied, including 20 astrocytomas, 4 oligodendroglioma, 2 anaplastic ependymoma, and 1 ganglioglioma. Autopsy brain tissue with reactive gliosis were used as control. Immunohistochemical staining using IDH1 and P53 antibodies was performed. The percentage positivity of tumor cells showing granular cytoplasmic staining was scored as 1 to 4 (0-25, 26-50, 51-75,76-100%), and staining intensity scored as 1 to 3 (low, medium, strong). A numerical IHC score for each case was derived by multiplying the percentage positivity score with intensity score.
Results: IDH1 immunopositivity was granular cytoplasmic, and seen in 7 of 20 astrocytomas of all grades (35%) and in all blastoma (1/6), anaplastic astrocytoma (2/6), astrocytoma grade 2 (4/5) and grade 1 (0/3). In contrast, all 4 oligodendrogliomas (100%) showed diffuse strong staining (3 grade-2, and 1 grade-4). No staining was observed in ependymoma (2), ganglioglioma (1) or reactive gliosis (9). IDH1 staining was much more intense in oligodendroglioma as compared with the majority of astrocytomas (*p=0.0003*). The expression of IDH1 and p53 proteins in 7 astrocytoma cases was similar (t-test, *p=0.446*), whereas the pattern was reversed in 3 oligodendrogliomas with high expression of IDH1 but low p53 protein (*p=0.003*).
Conclusions: Our study supports the observation that IDH1 may be an early event in the development of diffuse glioma, and further shows that IDH1 likely contributes more to the tumorigenesis of oligodendroglioma than astrocytoma, in contrast to

p53. IDH1 is neither expressed in reactive gliosis nor in majority of glioblastomas. Therefore IDH1 alongside p53 carries the potential to be a diagnostic marker of low-grade diffuse glioma.

Ophthalmic

1641 Biopsy Negative Temporal Arteries.
AM Bartlett, CT Welsh. Medical University of South Carolina, Charleston.
Background: Giant cell arteritis is the most common form of systemic vasculitis in older adults. The major therapy, prednisone, holds more risk for this age group even than it does in younger patients. The alternative, however, can be permanent visual loss. The literature indicates a range in negative biopsies up to 2/3. Our impression has been that of a much higher negative rate at our institution.
Design: We conducted a retrospective review of all temporal artery biopsies from 1995 to 2010 to determine the actual positive rate, related differences in biopsy material, and any possible clinical associations.
Results: Temporal artery biopsies from 1995 to 2010 numbered 244 total, with 19 displaying active inflammatory infiltrates (8%), 10 demonstrating medial scars (4%) consistent with prior injury to the artery (possibly treated arteritis, and 20 with adventitial perivascular lymphocytic cuffing. Bilateral biopsies were done simultaneously in 99 patients, with both active in 7 (7%), and both negative in 84 (85%). Activity was seen in only one of the two biopsies in 2 patients (2%), and medial scarring in one of two biopsies in two patients (2%). Two patients were biopsied twice with a medial scar in only one of the two (1%), and medial scar followed by active arteritis in 1 (1%). Length of biopsy was surgeon dependent; half the active arteritis biopsies were less than 1.5 cm and half greater than 2 cm. The biopsies containing medial scars were all over 2.7 cm. Biopsies which did not show histologic evidence of activity tended to be larger in general, presumably due to the surgical impression of a lack of focal nodularity.
Conclusions: Only 8% showed active signs of arteritis, and 4% demonstrated medial scars consistent with prior injury suggesting treated arteritis. Even combined, this is still only 12% of biopsies with any suggestion of arteritis, which is considerably lower than reported in the literature. Larger biopsies were no more likely to show active inflammatory changes than quite small biopsies, but medial scars tended to be picked up on larger biopsies. This would tend to indicate that surgeons can intra-operatively identify grossly active lesions. We will compare and contrast the clinical features of the patients with positive and negative biopsies to explain the discrepant rates at which these patients are being referred for biopsy.

1642 Morphoproteomics Provides Correlates of Chemoresistance, Metastatic Potential, Insulin-Like Growth Factor and c-Met Signaling in Uveal Melanoma with Therapeutic Implications.
RE Brown, J Buryanek. University of Texas- Medical School, Houston.
Background: Uveal melanoma has a propensity to metastasize to the liver and to be chemoresistant (systemic therapies produced a response rate of <1% in one large study).Insulin-like growth factor(IGF)-1 receptor (R)and c-Met are expressed in uveal melanoma and are significantly associated with metastatic disease and death. Moreover, these are receptors for IGF-1 and hepatocyte growth factor ligands, which are produced by the liver.The majority of uveal melanomas expressed activated MET protein in one study, and the blocking of MET reduced uveal melanoma cell proliferation and migration. Targeting IGF-1R and c-Met has been proposed as a therapeutic option in uveal melanoma.
Design: Three(3)patients with uveal melanoma with metastatic disease(two with metastasis to the liver) were the subject of this study. Representative sections were analyzed using a comprehensive morphoproteomic profile(Brown, RE.*Arch Pathol Lab Med.* 2009;133:568-79). This included a specific focus on chemoresistant and metastasis-associated protein analytes and on molecules linking IGF-1R and c-Met signaling in uveal melanoma, in an attempt to provide therapeutic opportunities.
Results: The anti-apoptotic protein, Bcl-2 was expressed in the cytoplasm of all tumor cells (up to 3+ on a scale of 0 to 3+) with concomitant and correlative expression of CD44 and heat shock protein(Hsp)90 on their plasmalemmal aspect and in their cytoplasmic compartment, respectively. Fatty acid synthase [FAS] expression(up to 2 to 3+) in the cytoplasm was evident in the vast majority of the tumor cells in each case.
Conclusions: Bcl-2 expression provides one explanation for the chemoresistance of uveal melanoma. Because CD44 and Hsp90 contribute to its expression, these present therapeutic opportunities. CD44 is associated with metastasis in melanoma. FAS represents a bridge between IGF-1R and c-Met, being induced at the genomic level by the former and also involved in the expression of c-Met tyrosine kinase. Inhibition of IGF-1R causes regression and attenuates invasion of uveal melanoma cells. Inhibition of FAS retards growth and induces apoptosis of melanoma cells and suppresses c-Met receptor kinase expression. The constellation of findings from our study raises the following therapeutic opportunities in uveal melanoma based on their reported actions: Valproic acid to downregulate CD44 and thereby, Bcl-2; 17-AAG to inhibit Hsp90 and also downregulate Bcl-2; Metformin to inhibit both IGF-1R signaling and FAS expression.

1643 Fine Needle Aspiration Biopsy of the Eye: A Single Institution's Experience.
G Levy, C Theoharis, D Chhieng, M Materin, G Cai. Yale University School of Medicine, New Haven, CT.
Background: Typically, a microscopic diagnosis of tumor is required prior to treatment. Treatment decisions of intraocular lesions, however, are often based on clinical examination due to the difficulty and potential complications in performing