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# 11TH BIENNIAL CANADIAN NEURO-ONCOLOGY MEETING

**MAY 28-30, 2004**
**TORONTO • ONTARIO • CANADA**

# ABSTRACTS

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# ABSTRACTS

## BASIC SCIENCE

**BSc-1**

### Antitumor activities of cytokine-induced killer (CIK) cells against human glioma in vitro

*Z-P Chen*, L Lin, (Guangzhou, Guangdong, China)*

Immunotherapy has been considered as an effective adjuvant for cancer therapy, however, its efficacy, such as systemic using lymphokine-activated killer (LAK) cells for glioma patients, was unsatisfactory. The obstacle could be CNS an immunologically privileged site or poor anti-glioma activity of the LAK cells. Thus, local delivery of immune active cells has theoretical advantage. In order to apply more active immune cells for local treatment of gliomas, we have generated cytokine-induced killer (CIK) cells by incubation of peripheral blood monocytes from glioma patient, and the anti-tumor activity of the CIK cells were tested. The activity of the CIK cells against glioma cells, at effector:target (E:T) cells ratio of 25:1, 50:1 and 100:1, as expressed by cell kill rate, was 37.12%, 60.69% and 71.08%, respectively. At E:T ratio of 50:1, the tumor cell kill rate of CIK cells on the 10, 18, and 26 days was 52.39%, 67.31% and 58.89%, respectively. The antitumor activity, at E:T ratio of 50:1, of CIK cells (67.31%) was significantly higher than that of LAK cells (55.76%). Our current results indicate that CIK cells derived from glioma patient could be efficiently employed as an adjuvant immunotherapeutic strategy for local treatment of glioma patient.

**BSc-2**

### The hypoxia-inducible cell death gene BNIP3 is mutated in malignant gliomas

*P Baijal, T Burton, S Zhang, E Henson, N Bristow, M Fonseca, SB Gibson, DD Eisenstat* (Winnipeg, Manitoba)*

Astrocytic tumors are the most common brain tumor. Glioblastoma multiforme (GBM, WHO grade IV) represents the most malignant form of astrocytoma with a time to progression of 12 weeks without intervention and 12-15 months survival with multimodality therapy. Response to therapy may be due to tumor hypoxia facilitating resistance to radiation and chemotherapy. The BCL2 nineteen kilodalton interacting protein, BNIP3, a Bcl-2 family member up-regulated in hypoxic regions, is activated by HIF1 alpha and mediates cell death in a caspase-independent manner through interaction of its transmembrane (TM) domain with mitochondria. BNIP3 is expressed in malignant astrocytes and is up-regulated in GBM, correlated with increased HIF1 alpha and glut-1 that indicate hypoxic regions within these tumors. In 33% of primary GBM we have detected mutations in BNIP3, confirmed by SSCPor by allele-specific PCR, that result in a truncated protein lacking a functional TM domain. BNIP3 over-expression in glioma cells induces cell death whereas treatment with antisense, dominant negative or mutant BNIP3 blocks hypoxia-induced cell death, due to failure of BNIP3 to localize to the mitochondria and inhibition of BNIP3-mediated mitochondrial dysfunction. We suggest that BNIP3 acts as a tumor suppressor and selective pressure within the tumor generates BNIP3 mutations providing a survival advantage. Our discovery could explain why treatments for malignant gliomas are often ineffective in hypoxic regions of these tumors.

**BSc-3**

### Genome profiling of medulloblastoma (MB) using array-based comparative genomic hybridization (A-CGH)

*A Huang*, B Behesti, C Hawkins, M Zielenska, E Bouffet, J Rutka, J Squire (Toronto, Ontario)*

It remains unknown whether distinct genetic features of infant MB underlie the higher incidence of metastatic disease and poorer outcome in this age group. We undertook a pilot study to compare the genomic profiles of 7 infant MB (diagnosed at ≤ 3 years of age) to 5 non-infant MB (diagnosed at > 3 years of age) by A-CGH. DNA from frozen or paraffin embedded tissue were hybridized to commercial genomic arrays (Human BAC array, Spectral Genomics, USA) containing nonoverlapping genomic clones separated by an average 1-4 megabases. Our data corroborated alterations in large genomic segments as reported previously by conventional CGH studies of MB. In addition we identified many small genomic regions with recurrent copy number gains and losses. Regions with DNAcopy number gains included chr 5p15: a region encompassing the hTERT gene, chr 8q24.2 associated with c-myc oncogene amplification, 1p36.33, 7p22.3, 7q32-33, 8p23.1, 9q34.3, 12p13.32 and 20q13.3. Regions with DNA copy number losses included chr 3p25.2, 6q14.1 and 10q23-25. Although infant and non-infant tumours generally showed similar changes in large chromosomal segments, copy number changes unique to each group were also identified. Studies to validate these observations and further delineate regions of change are underway.



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**BSc-4**

### Identification of a novel c-myc protein interactor with a potential role in medulloblastoma transformation

*A Huang*, D Picard, C Ho, R Ponzielli, L Penn (Toronto, Ontario)*

The Myc oncoprotein, a potent mediator of neoplastic transformation in diverse cell types, is commonly activated in medulloblastoma. The significance of Myc activation in medulloblastoma is underscored by observations that medulloblastoma tumours with c-myc genomic amplification or elevated mRNA expression correlate with poorer survival and more aggressive tumour phenotypes. In order to gain insights into how Myc protein function may be enhanced in medulloblastoma we sought to identify novel Myc protein partners by interrogating a medulloblastoma expression library using a bait encompassing the N-terminus transformation domain of c-myc. 32 putative novel Myc protein interactors with diverse predicted cellular functions were identified. HSC 44, a novel Myc interactor, that encodes a putative transcription factor, was characterized further to assess its contribution to Myc mediated transformation by stable expression in Rat1a fibroblast and UW228, an adherent medulloblastoma cell line. In soft agar colony forming assays, HSC 44 demonstrates weak transforming ability in Rat1a and UW228 cells, however, wild type Myc transforming activity is enhanced by stable HSC 44 expression in both cell types. Stable HSC 44 expression in Rat1a fibroblast also complements a transformation defective Myc mutant in soft agar assays. These observations support a functional link between HSC 44 and Myc in medulloblastoma transformation.

**BSc-5**

### Characterization of an interaction between ARF and the death domain-containing protein, DAXX

*S Ivanchuk*, S Mondal, J Rutka (Toronto, Ontario)*

The gene encoding the $p14^{ARF}$ tumour suppressor is deleted or altered in the majority of high grade glial tumours. While its role in MDM2-mediated stabilization of p53 is well-documented, recent studies have indicated $p14^{ARF}$ has additional cellular functions. We performed a yeast two-hybrid assay using full length $p14^{ARF}$ as bait to screen a human fetal brain cDNAlibrary in order to identify novel binding partners. One clone we identified encoded a portion of the death domain containing protein, DAXX. GST binding assays were performed to verify the interaction in mammalian cells. Furthermore, we mapped the regions of $p14^{ARF}$ and DAXX required for the interaction using co-immunoprecipitation analyses. Immunofluorescence analyses indicated that $p14^{ARF}$ and DAXX co-localize to discrete nuclear bodies upon co-transfection. Additionally, a fraction of endogenous $p14^{ARF}$ and DAXX colocalized at the nucleolar periphery in HeLa cells. Given DAXX's role as a transcriptional repressor, we performed promoter-reporter assays to assess the effects of $p14^{ARF}$ on DAXX's repressor capacity and found that $p14^{ARF}$ acts as a co-repressor. FACS analyses will be performed to determine the effects of $p14^{ARF}$ and DAXX expression on cell cycle profile in cell lines with or without functional p53 to further characterize the $p14^{ARF}$/DAXX interaction.

**BSc-6**

### Molecular dissection of a p21-Ras mouse model for astrocytoma

*D Kamnasaran*, A Guha (Toronto, Ontario)*

We have previously developed a mouse model for astrocytoma with activated p21-Ras in astrocytes. The progenies (RasB8) with a single copy transgene expression of activated p21-Ras in astrocytes develop multi-focal low and high-grade astrocytomas by 3 months. We hypothesize the activated p21-Ras allele creates susceptibility to the acquirement of additional genetic alterations leading to transformation. To investigate this hypothesis, astrocyte cell cultures from RasB8 and wild-type mice aged at P0, were established. Retroviruses encoding a Splice-acceptor type of gene trap vector were engineered and used to infect about 400,000 wild-type or RasB8 astrocytes with a multiplicity of infection of 1.5. Using soft agar assays, over one dozen transformed clones were identified from RasB8 gene trapped astrocytes, but none from gene trapped wild-type astrocytes. About 5-10% of RasB8 astrocytes (3 months old, not infected) and >90% of RasD7 astrocytes (2 wks old, multiple p21-Ras transgene overexpression, not infected) showed *in vitro* transformation, but none for uninfected RasB8 (P0) and wild-type (P0) astrocytes. In summary, gene trapping was used to randomly create additional genetic alterations in RasB8 (P0) astrocyte cells leading to transformation. The presence of the gene trap cassette has allowed for the identification of additional genetic alterations in activated p21-Ras astrocytes, which will be presented.

**BSc-7**

### TrkAinduces the death of neuroblastoma cells, and does so via a p53-dependent mechanism

*J-F Lavoie* (Toronto, Ontario); L LeSauteur (Montreal, Quebec); J Wong (Montreal, Quebec); CJ Thiele (Bethesda, Maryland); DR Kaplan (Toronto, Ontario)*

Neuroblastoma (NB) is the most frequent extra-cranial solid tumor of children. The best marker of favorable prognosis of NB is high expression of the TrkA/nerve growth factor receptor. To explore the molecular basis of why TrkAis a good prognosis marker, we examined the effect of expressing this receptor in human NB cells derived from poor prognosis tumors, and that had little or no endogenous TrkA. TrkAinduced the apoptosis of all tested NB cells lines, while expression of kinase-inactive TrkAor TrkB, the latter a marker of poor-prognosis marker neuroblastoma, did not. TrkA expression increased the levels of nuclear p53, p21Waf-1 (a target of p53 activity), and of cleaved caspase-3, and reduced the levels of the pro-survival protein Bcl-2. Expression of the anti-apoptotic protein $Bcl\text{-}X_L$ or treatment with a caspase inhibitor prevented TrkA-induced cell death. The apoptosis-inducing activity of TrkArequired wild-type p53, as a NB cell line encoding a nonfunctional mutant p53 was resistant to TrkA-mediated death. These results suggest that TrkA induces the apoptosis of NB cells by a p53-dependent mechanism, and that a reason why TrkA is a favorable prognosis marker for neuroblastoma is that high expression of TrkA is deleterious to this tumor's survival.



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**BSc-8**

### *In vitro* testing of starch nanospheres, a novel drug delivery system for malignant glioma

*M Loubani*, K Walsh, R Hammond, J Megyesi (London, Ontario); I McLennan (Lansing, Michigan)*

*Introduction:* One of the challenges to chemotherapy in cases of malignant glioma has been overcoming the blood brain barrier. Achieving therapeutic intratumoral concentrations using systemic chemotherapy has often been limited by adverse systemic reactions. In the present study, we describe a novel sugar-polymer nanosphere, which has been used to successfully encapsulate carmustine (BCNU) and doxorubicin (Dox). The encapsulated nanospheres have the potential to overcome the adverse effects of systemic drug delivery by intratumoral implantation.

*Methods:* Nanospheres 130-170 nm in diameter were produced from polysaccharides using a high shear method. These nanospheres form stable dispersions in saline up to 40 percent (w to w). Nanospheres were then used to encapsulate either BCNU or Dox, which were assayed for loading efficiency and then tested against free BCNU or free Dox to determine their relative cytotoxicities on U-251 and U-87 glioma cell lines.

*Results:* Dox and BCNU encapsulated nanospheres were produced with a loading efficiency of 1 percent (w to w). Both nanosphere types showed cytotoxicities comparable to the free BCNU or free Dox. The mechanism of cytotoxicity was found to be purely apoptotic as determined by immunohistochemistry using caspase-3. LDH assays showed no release of LDH with BCNU encapsulated, Dox encapsulated, or control nanospheres tested against U-251 and U-87.

*Conclusions:* The encapsulation of BCNU or Dox was carried out successfully in polysaccharide-based nanospheres, while preserving the cytotoxicities of both drugs.

Supported by NCI FLAIR Grant R43 CA92817.

**BSc-9**

### GLI2 as an oncogene in medulloblastoma

*TG Mainprize*, S Ueda, MD Taylor, A Ray, JTRutka (Toronto, Ontario)*

The Hedgehog (HH) signaling pathway was been shown to be involved in the formation of medulloblastoma (MB) through familial cancer predisposition syndromes, gene mutations and animal models. Mutations that either activate positive regulators or inactivate negative regulators in the HH pathway have been associated with sporadic MB. GLI2 is the major effector regulator of this pathway because it serves as both a transcriptional repressor or activator and as such, may play a large role in MB oncogenesis. Using molecular techniques, we have elucidated some of the factors regulating GLI2 activity. We first cloned the N-terminus of human GLI2 which has not been previously described. Using the full-length GLI2 and the dominant-active N-terminally deleted GLI2, we showed that the ability negative regulators SUFU and SKI to regulate GLI2 function resided in the N-terminus. However, phosphorylation of GLI2 by protein kinase A can inhibit transcriptional ability of both the full length and the dominant-active form using an 8XGLI-luciferase reporter construct. Mutational analysis of 30 different MB specimens was performed with a single point mutation being found in the N-terminus. In conclusion, we have cloned the full length GLI2 and demonstrated its regulation by various transcriptional regulating molecules.

**BSc-10**

### Overexpression of MARCKS in EGFRvIII expressing glioblastoma multiforme (GBMs)

*J Micallef*, J Caldwell, M Moran, A Guha (Toronto, Ontario)*

*Introduction:* The most common gain of function mutation in GBMs are amplification/over-expression of the wild-type (wt) and mutated epidermal growth factor receptors (EGFRs), the most common of which is EGFRvIII. The differential signaling pathways utilized by EGFRvIII vs. wt-EGFR, which may contribute to its more aggressive behavior is not well-known.

*Methods:* A novel differential mass spectral analysis termed ICAT, was used to examine the differential protein profile of GBMs harboring EGFRvIII vs. GBMs that only express wt-EGFR.

*Results:* From the ICATanalysis, MARCKS, a protein previously implicated in breast cancer invasion, was identified to be markedly increased in EGFRvIII vs. wt-EGFR expressing GBMs. To verify this ICAT finding, standard western immunoblot analysis using MARCKS antibody was undertaken on a larger panel of GBM cell lines (Tet-Off expression of EGFRvIII), GBM xenografts (± EGFRvIII) and GBM operative specimens (± EGFRvIII).

*Discussion/future directions:* This study demonstrates proteomic based technologies ability to identify differences at the level of the proteome, between different sub-types of human diseases, such as GBMs. Current work involves assessing the functional role of MARCKS in GBMs. MARCKS is being down-regulated in GBMs expressing EGFRvIII and increased in GBMs expressing only wt-EGFR. If the *in vitro*/*in vivo* functional assays demonstrate MARCKS involvement in promoting the aggressive biology of EGFRvIII expressing GBMs, then it may be an additional GBM specific biological target.

**BSc-11**

### The cloning and characterization of proteins binding to glial cells missing

*S Mondal*, S Ivanchuk, G Boulianne, J Rutka (Toronto, Ontario)*

Mammalian brain development is a complicated process involving a variety of molecular factors and signaling pathways. Cancer-causing mutations affecting glial cells lead to the most common solid tumour; glioblastoma multiforme. Studying the molecular basis of glial cell development during embryogenesis will help the understanding of changes that lead to malignant transformation in glia. The central nervous system in fruit flies is very well-characterized and its development resembles a more simplified version of mammalian CNS development. In Drosophila melanogaster, the common fruit fly, a single nuclear protein, glial cells missing (gcm) is the master regulator of lateral glial cell development, commanding the expression of genes that cause glial differentiation. Mutant flies with inappropriate gcm expression lack glial cells and die during embryogenesis. Because nuclear factors often require binding to various other proteins to initiate downstream gene activation, we screened a fetal brain cDNAlibrary using the yeast two hybrid method and are currently analyzing



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potential gcm-interacting proteins. The interactions of gcm with isolated binding proteins may regulate effects of gcm activity during development. Following the confirmation of binding to gcm, we will utilize techniques involving Drosophila genetics to determine the functional consequence of each interaction in glial cell development.

**BSc-12**

**High-resolution genetic alteration map of transformed Schwann cells in peripheral nerve tumors (PNTs)**

*A Pandita*, L Bereskin, N Sabha, P Shannon, A Guha (Toronto, Ontario)*

Neurofibromas are composed of transformed Schwann cells, with the primary bi-allelic inactivation of Nf1 and neurofibromin expression. Sub-types of neurofibromas differ in their biological properties, with low-resolution CGH studies to date on entire neurofibromas consisting of several cell types, not yielding a thorough understanding of the molecular differences between the transformed Schwann cells in these neurofibromas. In this study, Schwann cells are isolated from peripheral nerve tumors (PNTs) using Laser Capture Microdissection (LCM), to isolate and amplify microquantities of DNAand mRNA. Isolated Schwann cell DNA are analyzed with ArrayCGH, using BAC-arrays with a ~1MB resolution. Preliminary results reveals plexiform neurofibromas have more losses in comparison to malignant PNTs, indicating alternate genetic pathways. For malignant PNTs, previously reported CGH alterations involving chromosomes 8,12,17 and 19 were detected, plus novel high copy gains on chromosomes 2q33 and 3q25. In matched frozen specimens, RNA from Schwann cells has been isolated and is currently being tested for specificity and quality, before analysis by microarrays. These array results will be confirmed using FISH and/or real time PCR on the specimens and serve to increase our understanding of the genetic differences in the Schwann cells in different neurofibroma sub-types, an area of molecular diagnostic/prognostic and potential therapeutic importance.

**BSc-13**

**Downregulated in renal cell carcinoma, a novel effector of glioma invasion**

*K Petrecca*, A Angers-Loustau, R Waldkircher, MS Sadr, J Wang, RF Del Maestro (Montreal, Quebec)*

Malignant glial cell invasion represents a major obstacle in the treatment of glial-derived brain tumors. In order to uncover molecular mechanisms that play a role in invasion we developed a novel functional screening assay to identify genetic determinants of invasion. We identified downregulated (drr-1) in renal cell carcinoma as a candidate effector of invasion and show that it mediates a 250% increase in invasion in a 3D tumor model. Immunohistochemical analysis of human tissue shows that normal brain and non-invasive gliomas exhibit little to no detectable drr1 expression whereas invasive gliomas exhibit abundant drr1 immunoreactivity. We also show that drr1 colocalizes with the actin cytoskeleton and have identified a domain required for actin association. Mutation of this domain shifts drr1 expression from the actin cytoskeleton to the microtubular cytoskeleton. We identified Map1A, a rapid inducer of tubulin polymerization, as a drr1-interacting protein that links drr1 to the microtubular cytoskeleton. Taken together, we show that drr-1 is an actin-microtubular crosslinker that promotes glial cell invasion *in vitro* and is overexpressed in invasive human gliomas. We propose that drr1 is a strong effector of human glioma invasion. Further identification of drr1 signaling pathway members may yield novel therapeutic targets.

**BSc-14**

**Mutant epidermal growth factor receptor (EGFRvIII) potentiates development of gliomas in transgenic mouse models**

*Q Wei, L Clarke, N Sabha, B Qian*, J Lavoie, P Shannon, D Kaplan, D Gutmann (St. Louis, Missouri); A Guha (Toronto, Ontario)*

EGFRvIII mutant is common in high- but not low-grade gliomas. Using ES transgenesis we showed EGFRvIII could not induce, but could potentiate glioma formation when bred to our glioma pre-disposed GFAP-V$^{12}$Ha-Ras mice. These double transgenics died at ~3-4wks from oligodendrogliomas vs. mainly astrocytomas in the GFAP-V$^{12}$Ha-Ras alone. Here effect of post-natal expression of EGFRvIII in normal and glioma susceptible mice is examined.

GFAP-V$^{12}$Ha-Ras mice (1mth) and normal littermates frontal lobes were injected with adenoviral EGFRvIII (Ad:EGFRvIII) or control Ad:GFPand brains examined 4wks post-injection.

Ad:EGFRvIII or Ad:GFP into normal mice did not result in gliomas. Ad:GFP injected GFAP-V$^{12}$Ha-Ras mice had few low-grade astrocytomas as previously noted in these mice. However, Ad:EGFRvIII injected GFAP-V$^{12}$Ha-Ras transgenics developed large confluent low- and many high-grade gliomas, which were mainly astrocytomas or oligo-astrocytomas. EGFRvIII expression was detected only in the astrocytes &/or oligodendrocytes in these high-grade gliomas and not in their low-grade counterparts.

Similar to our results with ES transgenesis, post-natal EGFRvIII does not induce gliomas. EGFRvIII does potentiate gliomagenesis in a susceptible astrocyte, such as one expressing V$^{12}$Ha-Ras. The subtype of glioma that arises from this EGFRvIII potentiation depends on the differential potential of the transformed cell. Embryonic EGFRvIII expression resulted in mainly oligodendro-gliomas vs. mainly astrocytomas with post-natal expression, similar to adult human gliomas. Ongoing experiments are directed towards understanding the role of EGFRvIII in gliomagenesis in the background of other relevant genetic alterations, such as loss of Ink4a/Arf and Pten.

**BSc-15**

**Pathological and molecular progression of astrocytomas in a GFAP:$^{12}$V-Ha-Ras mouse astrocytoma model**

*N Sabha*, P Shannon, N Lau, D Gutmann (St. Louis, Missouri); A Guha (Toronto, Ontario)*

We have created an astrocytoma model using embryonic stem cell transgenesis of GFAP:$^{12}$V-Ha-Ras. These mice are born normally, but develop and die from multifocal astrocytomas, commencing approximately 12-14wks post birth. To gain insights into the pathological and molecular development of the astrocytomas, we examined these transgenic mice at E16.5day, 1, 3, 4, 8 and 12wks after birth.

At E16.5day, the $^{12}$V-Ha-Ras transgene was expressed, however,



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the transgenic and control littermates were similar. Diffuse astroglial hyperplasia, with GFAP+'ve/Nestin-'ve cells in the subpial and periventricular regions at 1wk, was the first differentiating feature. Low grade GFAP+'ve/Nestin+'ve multifocal astrocytomas with nuclear atypia were detected at 3wks. In addition to VEGF, a subset of these astrocytoma cells expressed epidermal growth factor (EGFR). At 12wks, 40% of the mice harbored multifocal astrocytomas, with one mouse succumbing to a high-grade astrocytoma, characterized by cytological atypia, increased vascularity, with regions of necrosis and hemorrhage. These tumors had decreased expression of PTEN, with increased levels of phospho-MAPK and phospho-Akt. Several missense mutations in the DNA and tetramerization domain of p53 were detected in the low and high grade tumors, in conjunction with increased p53 staining.

We postulate that transgenic expression of activated p21-Ras in GFAP+'ve glial precursors, leads to genetic instability and diffuse astroglial hyperplasia, but not transformation. Additional acquired molecular alterations are involved in formation of low-grade and subsequent progression to high-grade astrocytomas. These molecular progression pathways in the transgenic model have similarities to those in human astrocytomas, further validating its potential use as a pre-clinical reagent in neuro-oncology.

**BSc-16**

**The role of ROCK inhibition on astrocytomas**

*B Salhia*, J Rutka (Toronto, Ontario)*

Malignant astrocytomas are highly invasive neoplasms infiltrating diffusely into regions of normal brain rendering total surgical extirpation impossible. The intracellular mechanisms governing invasion, while poorly understood, presumably include modifications of the cytoskeleton. The Rho-GTPases (Rac, Cdc42 and Rho) are pivotal regulators of cytoskeletal organization and cell motility. Several studies have demonstrated that activation of RhoA or its effector, Rho-kinase, leads to increased tumour cell invasiveness. In contrast to many studies demonstrating that Rho-kinase inhibition with Y27632 or dominant-negative constructs leads to decreased invasion and motility of hepatoma, prostate and breast cancer cells, Rho-kinase inhibition stimulated the motility of U251 and U87 glioma cells. We have also shown that U251 and U87 glioma cells treated with Y27632 or the dominant-negative mutant displayed dramatic morphological and cytoskeletal alterations characterized by stellation, an increase in the number and length of cell processes, inhibition of actin polymerization, longitudinal reorientation of microtubules and aggregation of intermediate filaments. These results shed new light on our current understanding of Rho signaling within the context of glioma cell motility and underscore the importance of understanding points of convergence with other members of the Rho family. The findings of these and future studies will be of therapeutic benefit to managing glioma invasion.

**BSc-17**

**Molecular genetic characterization of serial tumour specimens from a long-term survivor of glioblastoma multiforme**

*D Saltman* (Hamilton, Ontario); S Kamel-Reid (Toronto, Ontario); J Wells, J Provias, M Sur, S Sagar, H McCarter (Hamilton, Ontario)*

Long-term survivors (LTSs) of glioblastoma multiforme (GBM) are uncommon, with less than 10% of patients alive three years after initial diagnosis. Loss of heterozygosity (LOH) for chromosome 19q has been described as a positive prognostic factor for LTSs of GBM, while LOH of chromosome 10q appears to be a present more frequently in short-term survivors. The loss of 1p is thought to be infrequent in GBM. Serial molecular and histopathological studies in LTSs of GBM provide a unique opportunity to correlate genetic aberrations with clinical outcome. We have analyzed serial tumour specimens from a LTS of glioblastoma for LOH of 1p, 10q and 19q by polymerase chain reaction (PCR) amplification of microsatellite markers. The tumors at diagnosis in 1997 showed 1p LOH, 10q LOH and 19q LOH. The first relapse specimen had no loss of 1p, but had 10q LOH and 19q LOH. The second relapse specimen from 2003 demonstrated 1p LOH and 19q LOH but no longer had 10qLOH. The presence of tumor clones containing 1p and 19q LOH in the initial resection specimen may be associated with long-term survival in this GBM patient. The LOH for chromosome 10q at diagnosis did not predict a short survival.

**BSc-18**

**Identification of a human brain tumourstem cell**

*SK Singh*, ID Clarke, C Hawkins, T Hide, MD Cusimano, PB Dirks (Toronto, Ontario)*

*Introduction:* We recently reported the identification of a brain tumor stem cell (BTSC) from primary human brain tumors of different phenotypes. In this study, we explore whether the BTSC is capable of initiating and maintaining a tumor *in vivo*.

*Materials and Methods:* Six brain tumours (adult and pediatric) were acutely dissociated and subjected to cell sorting for the neural stem cell marker CD133. The isolated CD133+ and CD133- cell populations were injected into the frontal lobes of 6-week old NOD-SCID. Mice were followed with interim MRI imaging, and on sacrifice at 23 weeks, brains were examined for histology and immunohistochemistry.

*Results:* For all tumours studied, mice injected with CD133+ BTSCs showed tumours on histology. An *in vivo* limiting dilution performed with CD133+ medulloblastoma BTSCs showed that as few as 1000 CD133+ cells were capable of initiating large anaplastic tumours. Tumours showed positive immunostaining for the CNS stem cell marker nestin and did not stain for differentiated cell markers. Mice injected with CD133- cells never developed tumours.

*Conclusions:* The CD133+ BTSC from brain tumours of different phenotypes is exclusively capable of initiating a tumour with high potency *in vivo*. Future therapies may be targeted at the tumour-initiating BTSC rather than every cell in the tumour.

**BSc-19**

**CNS developmental abnormalities induced by astrocyte-specific Pten deletion**

*Wei Q*, L Clarke, B Qian, C Zhang, P Shannon, D Gutmann (St. Louis, Missouri); A Guha (Toronto, Ontario)*

Loss of Pten is prevalent in high- not low-grade astrocytoma. Neuronal deletion of Pten in mice embryonically caused early post-natal death, without glioma development. Here, we created and characterized an astrocyte specific GFAP-Cre mouse to examine role of Pten in gliomagenesis.



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Pro-nuclear injection was used to create a GFAP-Cre mouse, with Cre-excision in astrocytes characterized by double transgenics with Z/AP reporter mice. Double transgenics with the GFAP-Cre X PTEN$^{flox/flox}$ mouse (from Dr. Tak Mak) was created.

GFAP-Cre X PTEN$^{flox/flox}$ mice died from seizures with enlarged brains and failure to thrive by 2-6wks. Loss of Pten resulted in activated P-Akt, mainly in astrocytes and not neurons, Purkinje cells or oligodendrocytes. The Pten-'ve astrocytes were increased in numbers and size, though no gliomas were noted. Multiple and reproducible structural CNS abnormalities were noted. The cerebellum was enlarged with abnormal radial glia and disorganized but normal Purkinje cells. The hippocampal neurons were increased in number and size, with a gradient of increasing Pten expression, inversely correlated to P-Akt expression, towards the cortical surface.

Even with mainly astrocyte specific Cre-excision of Pten, CNS developmental alterations resulted in early peri-natal death, without any glioma formation. Loss of Pten resulted in increased P-Akt with increased cell size and hyperplasia, but not transformation. Strategies for *in vivo* somatic deletion of Pten in mouse astrocytes are therefore being pursued with inducible-Cre mice and adenoviral Cre injections with the PTEN$^{flox/flox}$ mice alone, or in the context of mice harboring additional genetic alterations relevant to gliomas that we have created or obtained.

**BSc-20**

### The role of Slit/Robo in medulloblastoma vs. glioma cell invasion

*TE Werbowetski* (Montreal, Quebec); R Bjerkvig (Bergen, Norway); Y Rao (St. Louis, Missouri); R Del Maestro (Montreal, Quebec)*

Chemotropic cues such as the slit, netrin and semaphorin families guide the migration of neuronal and glial cell precursors during neural development. Recently slit, and its receptor Robo (Roundabout) have been implicated in tumour angiogenesis and leukocyte migration. It is not known if these molecules contribute to directing the invasion of brain tissue by medulloblastoma and glioma cells.

Here, we provide evidence that medulloblastoma cells are inhibited, but not repelled, by a localized concentration of slit-2 in collagen gels as demonstrated by time-delayed co-culture and sodium alginate bead microencapsulation culture. Slit-2 had no effect on glioma cell invasion. Medulloblastoma cell lines express slit-2, and its receptor Robo-1, and both functional blocking antibody and dominant negative Robo experiments demonstrate a 50% rescue of the invasive phenotype compared with slit treatment alone. Studies are currently underway to assess the effect of overexpressing Robo-1 in glioma cell lines with the hope of inducing a significant inhibitory effect on invasion after introducing exogenous slit-2.

Our findings indicate that the effect of slit-2 is not conserved for all types of brain tumours, and that manipulation of Slit-Robo signaling may serve as a potential anti-invasive treatment for medulloblastoma tumours.

**BSc-21**

### Collaborative role of Ang1 and VEGFin modulating astrocytoma angiogenesis

*G Zadeh*, L Pillo, R Reti, P Shannon, A Guha (Toronto, Ontario)*

VEGF and angiopoietins are two endothelial cell (EC) specific angiogenic factors that collaborate in a highly orchestrated manner to regulate normal vessel development. However, their interactive role in tumor angiogenesis is not yet understood and this study focuses on investigating the collaborative role of VEGF and Ang1 in astrocytoma angiogenesis.

In both subcutaneous and intracranial models of astrocytoma using U87 and U373 cell lines, we co-modulated the expression of Ang1 and VEGF. We found that Ang1 conferred a significant growth advantage to the tumors in the presence of VEGF by increasing tumor vascularity. With down-regulation of VEGF expression, however, Ang1 lost its proangiogenic impact and tumor growth remained unchanged compared to control. Our results demonstrate that Ang1 acts in a proangiogenic manner, regulating the vascular growth of malignant astrocytomas (MA) only in the presence of VEGF. These findings highlight the close interactive role of Ang1 and VEGF in MA and suggest that the most efficacious anti-angiogenic treatment should target both pathways. An additional observation is that Ang1 leads to vascular changes resembling the characteristic 'tufting' process seen in human MA. This is the first evidence in a tumor model identifying Ang1 as a molecular regulator for the 'tufting'process seen in MA.

**BSc-22**

### High-resolution longitudinal screening with magnetic resonance imaging in a murine brain cancer model

*NA Bock, G Zadeh*, LM Davidson, B Qian, JG Sled, A Guha, RM Henkelman (Toronto, Ontario)*

One limitation of intracranial mouse models of disease is the inability to monitor and evaluate the intracranial compartment non-invasively over time. In this study, we have established protocols for multiple-mouse MRI to follow the growth and behavior of intracranial xenografts of gliomas longitudinally. We successfully obtained weekly 3D images on 16 mice bearing human U87 xenograft gliomas for a total of 5 weeks on a multiple-mouse MRI.

The overall survival of tumor-bearing mice included in the MRI screen was (33 ± 1 days) the same as the survival mice not included in the MRI screen (36 ± 5 days). These results confirm that MRI for follow-up of tumor growth of intracranial tumors is feasible and not detrimental to the outcome of the mice. The lesions detected on the MRI images were confirmed to be tumors by both Evans Blue and histology. An interesting and unexpected finding was high variability in tumor growth pattern, which provides invaluable insight into intracranial tumor behavior and has significant therapeutic relevance. This study establishes a protocol for high-throughput whole brain MRI to be used as a research tool for investigating the biology of both xenograft and transgenic mouse models of intracranial tumor.



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**BSc-23**

### Targeting the Tie2/Tek receptor in astrocytomas

*G Zadeh*, B Qian, A Okhowat (Toronto, Ontario); CD Kontos (Durham, North Carolina); A Guha (Toronto, Ontario)*

Tie2 is an endothelial cell specific receptor tyrosine kinase, whose activation is positively and negatively modulated by angiopoietin-1 and angiopoietin-2, respectively. Angiopoietin mediated modulation of Tie2 activation contributes to normal vessel development and stability, however, its role in tumor angiogenesis is not well-known. We investigated the role of Tie2 activation in malignant astrocytomas, a common and highly vascularized primary human brain tumor. We found that Tie2 expression and activation increases with increasing malignancy grade of astrocytomas. Inhibition of Tie2, using a kinase deficient Tie2 construct, decreases the growth of malignant human astrocytomas in both subcutaneous and intracranial xenografts. Tie2 inactivation disrupted the tumor vascularity, with a decrease in microvascular density, increased presence of abnormally dilated vessels and loss of interaction between endothelial cells and surrounding smooth muscle cells, all collectively resulting in increased tumor cell apoptosis. Overall, these findings strongly suggest that Tie2 activation contributes significantly to astrocytoma tumor angiogenesis and growth. We postulate that targeting Tie2 activation, either independently or in conjunction with other anti-angiogenic therapies, such as against vascular endothelial growth factor (VEGF), is of potential clinical interest.

# MEDICAL

**MED-1**

### Retrospective study of prophylactic anti-convulsive therapy for patients with glioblastoma multiforme (GBM) brain tumor

*M-C Beauchemin*, B Fortin, J-P Bahary (Montreal, Quebec)*

*Purpose:* To determine the toxicity and the effectiveness of long term prophylactic anti-convulsive therapy for patients with GBM in lowering the rate or delaying the occurrence of seizures.

*Methods:* Retrospective study of patients with GBM presenting at Notre-Dame Hospital, from January 1997 to December 2001.

*Results:* One hundred and six patients with GBM were identified. Of those, only 64 were given long term prophylactic anti-convulsive therapy (AC group). The 42 remaining patients represent the control group. Twelve patients in the AC group (19%), of which 8 (67%) had a sub-therapeutic AC blood level, had seizures, compared to 7 patients (17%) in the control group. The average time before the first seizure was 173 days for the AC group compared to 93 days for the control group. Nine of 64 patients in the AC group (14%) had minor toxic effects from therapy.

*Conclusion:* There was no reduction in the number of patients who had seizures with prophylactic anti-convulsive therapy, but the average time before the first event was longer. A sub-therapeutic AC blood level at the time of seizure probably contributed to the lack of effectiveness of the treatment but may also have reduced its toxicity.

**MED-2**

### Survival and outcome in patients with oligodendroglial tumors treated with radiotherapy and chemotherapy

*RM Costa*, N Laperriere, CS Wong, Q-L Yi, WP Mason (Toronto, Ontario)*

*Objective:* To evaluate the impact of radiotherapy and chemotherapy on survival and outcome in patients with oligodendroglial tumors.

*Patients and Methods:* 149 consecutive patients, median age 46 (range 24-84), diagnosed between 1989 and 2001 with the following pathologic diagnoses: 71 low-grade oligodendroglioma (LGO), 16 oligo-astrocytoma (OA), 62 anaplastic oligodendroglioma (AO). Following surgery, patients were observed, or received radiotherapy and/or chemotherapy.

*Results:* The median overall survival for patients with LGO was 10.6 years, for OA 8 years, and for AO 1.8 years. The median survival for patients with LGO who received only radiotherapy was 9 years, and 11 years for those who received chemotherapy after radiation failure (p=0.6496). The median overall survival for patients with OA treated with radiation alone was 5.2 years. The median survival for patients with AO treated with radiation alone or chemotherapy alone was 1.2 years, and 2.2 years for those treated with radiotherapy and chemotherapy (p=0.0720). The median time to progression (MTTP) for patients with LGO treated initially with radiotherapy alone was 6.1 years, and 2.5 years for those treated initially with chemotherapy alone (p=0.0061). For patients with AO, the MTTP was 0.8 years for those receiving radiation alone or chemotherapy alone, and 1.6 years for those treated with radiotherapy and chemotherapy (p=0.7561).

*Conclusion:* Radiotherapy remains a standard initial treatment for patients with oligodendroglial tumors, but increasingly these patients are receiving chemotherapy at some point during their illnesses. Early radiotherapy in LGO delays time to progression but does not influence survival. The addition of chemotherapy following radiotherapy extends survival in patients with LGO and AO. The use of chemotherapy alone as initial treatment for patients with both LGO and AO may not be as effective as radiotherapy in delaying disease progression.

**MED-3**

### High-grade glioma treated with temozolamide (TMZ) and 13-cis-retinoic acid (cRA) – A single institution study

*C Mihalcioiu, S Huszar, A Demers, G Schroeder, K Jones, K Vijay, R Rhodes, DD Eisenstat* (Winnipeg, Manitoba)*

A recent phase II study reported activity of TMZ and cRA for recurrent/progressive malignant gliomas with 32% 6 month PFS for glioblastoma multiforme (GBM) patients. From 2000-2003, we retrospectively analyzed adults with malignant glioma who received, following surgery and radiation therapy (RT) ± low dose TMZ (75 mg/m$^2$/d x 42d), TMZ (150-200mg/m$^2$/d, d1-5) and cRA (100 mg/m$^2$/d, d1-21) every 28d for up to 24 cycles or progression. Time to progression (TTP) was the primary end-point. Of 40 patients (31 GBM, 6 anaplastic astrocytoma, AA), 21 remain alive. 31/40 patients received TMZ/cRAas adjuvant therapy. 15/25 patients with RT alone and 3/15 patients who received chemoradiation have died.



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12/16 patients who progressed on RT died, confirming poor outcomes for this group. 40 patients received 298 cycles of TMZ/cRA; 7 patients received >10 cycles, but only 3 completed 24 cycles. Responses to TMZ/cRAwere documented in 15/40 patients (8 SD/7 PR). Median TTP was 27.2 weeks for RT alone and 31.7 weeks for RT/low dose TMZ, but was 18.5 weeks for patients who progressed on RT. Median OS for all 40 patients was 95.5 weeks but only 70.2 weeks for those who progressed on RT. Median TTP was 87.4 weeks for those with PR+SD but was 18.6 weeks for patients progressing on TMZ/cRA (p=0.0001). Our results suggest that TMZ/cRA prolongs TTP for patients with malignant gliomas and supports use of this regimen in a Phase III design.

**MED-4**

**Aglycone protopanaxadiol (aPPD) induces apoptosis of glioma cells with different PTEN and P53 status**

*GY Liu*, X Bu, H Yan, W Jia (Vancouver, British Columbia)*

Ginseng saponin Rh2 that exist in ginseng extract with trace concentrations has been known for its cytotoxicity on cancer cells. Here we investigated a Rh2 derivative, aglycone 20(S)-protopanaxadiol (aPPD) that can be obtained with lower cost, for its potency in cytotoxicity on glioma cells with different PTEN and P53 status. We also tested Careseng®, a specially formulated ginseng product mainly containing aPPD for its effect on glioma cells. U87MG (PTEN(-) and wild type p53) and SF188 (PTEN(+) and p53 mutant) were treated with different concentrations of aPPD or Careseng®. Our results demonstrated that both aPPD and Careseng®, as effectively as Rh2, rapidly induced apoptosis in two glioma cell lines. Caspase-3, -8, -7 and -9 were activated in SF188 cell lines. However, inhibition of caspase 8 partially blocked aPPD/Careseng® induced apoptosis on SF188 but not U87MG cells. Phosphorylated Akt on Ser473 was decreased in PTEN(-) U87MG but not PTEN(+) SF188 cells. aPPD/Careseng® caused increase in concentrations of superoxide anion in both cell lines and antioxidant tert-butylhydroquinone (tBHQ) partially blocked apoptosis. These results showed that aPPD is a potential apoptotic anticancer agent. Apoptosis induced by aPPD could be mediated by different mechanisms depending on PTEN and P53 status of the cell.

**MED-5**

**Response of recurrent pilocytic astrocytoma in adults to temozolomide**

*DR Macdonald* (London, Ontario)*

Pilocytic astrocytomas (PA) are WHO grade I tumors that usually occur in children. Surgical resection is often curative. Incompletely resected PA are often treated with radiotherapy (RT). There is little information on chemotherapy in adult PA. Two adults with recurrent PA responded to temozolomide (TMZ). A man, age 54, had a cerebellar PA partly resected in 1995, then received RT. Multifocal recurrence was biopsy-confirmed in 2/2002. He received 12 cycles of standard oral TMZ (200 mg/m$^2$/day x 5 days, q 28 days). A partial response (PR) was seen after 6 cycles and a complete response (CR) after 12 cycles. He remains in CR 1 year off treatment. A woman, age 27, had partial resection of a right temporal PA in 1987. MRI progression was biopsy-confirmed in 1/2000 and treated with RT. Symptomatic MRI progression was treated with standard TMZ starting 11/2001. A minor response was seen after 9 cycles and PR after 12 cycles. She received 24 cycles of TMZ with continued PR. TMZ was well-tolerated in both patients. TMZ is active in PA, producing sustained responses, but prolonged treatment may be needed.

**MED-6**

**Low-dose temozolomide chemotherapy is active in recurrent malignant glioma, even following progression on conventional 5/28 day treatment: results of a practice audit**

*P Rizek, T Morrison, R Cashman, T Haller, J Perry* (Toronto, Ontario)*

*Background and Objective:* We report our experience with conventional and novel temozolomide (TMZ) schedules in patients (pts) with recurrent glioma.

*Design/Methods:* Retrospective review of all pts given TMZ from 1999-June 2003. Survival estimated using the Kaplan-Meier method and regression analyses done by a biostatistician using appropriate statistical methods (SAS 8.2 for Windows).

*Results:* 122 pts had 5/28 day TMZ (200mg/m$^2$, all previously untreated) at first progression. At second progression either a 21 day (50mg/m$^2$) or 28 day (continuous, 25mg/m$^2$) schedule was offered. Overall survival results were glioblastoma (GBM) n=59, MST 1.18 (0.96-1.32) years, anaplastic gliomas (AA, AO, AOA) n=44, MST 3.45 (2.36-7.56) yrs, and low grade glioma n=15, MST 7.20 (1.29-20.74) yrs. 85 pts had 5/28d TMZ alone, while 37 pts had 5/28d followed by low dose TMZ. MST for all pts was 1.67 yrs with conventional vs. 2.89 yrs with combined conventional and low dose treatment (log rank p=0.0115). Objective partial responses to all schedules were seen. Time to progression (TTP) for GBM was 19 (9.88-16.71) wks on conventional and 10.71 (8-32.29) wks on low dose therapy. TTP for anaplastic glioma was 27 (18.88-32.00) wks on conventional and 22.42 (7.71-36.7) wks on low dose therapy. Pts with anaplastic gliomas accounted for most of the variance in survival: MST 2.52 (1.85-3.50) yrs in 28 conventionally treated pts compared to a MSTof 9.52 (2.52-17.6) yrs in 16 pts treated with low dose TMZ, p=0.033. Controlling for age and tumour type, the expected time to death for those who received low dose therapy was 55% greater than for pts treated with 5/28 day TMZ alone. Karnofsky performance status was unavailable for many pts and could not be analyzed. Toxicities were mild in all groups. No opportunistic infections were detected.

*Conclusions:* Malignant gliomas that progress after conventional 5-day TMZ may respond to low dose TMZ; these responses may be related to the mechanisms of TMZ resistance. This retrospective study is limited by selection bias and incomplete recording of all prognostic variables, therefore a phase II prospective study testing this treatment approach is underway.



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# PEDIATRICS

## PEDS-1

### Surveillance spinal MRI in the follow-up of children treated with medulloblastoma

*UK Bartels*, M Shroff, U Dag-Ellams, N Laperierre, J Rutka, E Bouffet (Toronto, Ontario)*

*Background:* Standard follow-up of children treated for medulloblastoma includes regular cranial and spinal MRI. The role of surveillance spinal MRI has not yet been established.

*Purpose:* To study the predictive value of postoperative follow-up cranial MRI in determining the relevance of surveillance spinal MRI.

*Methods:* Patients diagnosed with medulloblastoma and subsequently followed in HSC between 1985 and 2003 were identified. Contrast-enhanced spinal MRIs, which were done concomitant with cranial MRIs (doublets) were reviewed. Recurrence was defined as any new abnormal lesion (in the brain or the spine) in a symptomatic or asymptomatic patient.

*Results:* Out of 122 patients, 63 patients (18F: 45M, median age: 6.6 years, median follow-up time: 4.3 years) had at least 1 evaluable doublet in the follow-up period. 275 doublets were available (median per patient: 3, range: 1-13). Of 244 doublets with negative cranial MRI, no new lesion was identified on spinal MRI. Of 31 cranial MRIs (23 patients) showing signs of recurrence/progression, 20 spinal MRIs showed nodular or leptomeningeal lesions.

*Conclusions:* Postoperative follow-up cranial MRI has a very useful value in predicting disease in the spine. Absence of progression on cranial MRI is highly predictive of a negative spinal MRI.

## PEDS-2

### Pilot study of vinblastine in patients with recurrent and refractory low grade glioma

*E Bouffet* (Toronto, Ontario); S Goldman (Chicago, Illinois); R Jakacki (Pittsburgh, Pennsylvania); ML Garre (Genoa, Italy); N Foreman (Denver, Colorado); E Cairney (London, Ontario); M Etzl (Phoenix, Arizona); N Tariq (Toronto, Ontario); D Hargrave (London, United Kingdom)*

*Background:* For low grade glioma (LGG) patients who show progression during or after a first line of chemotherapy, there is increasing interest in trying to delay radiation further by using second-line chemotherapy, particularly in younger children.

*Methods:* Weekly vinblastine (6 mg/m$^2$/once a week) was given for 52 weeks in patients with recurrent/refractory LGG. Response was assessed at 10 weeks, 6, 9 and 12 months.

*Results:* 20 patients (9 males 11 females, median age 7 years – range 1.4 to 16) were included in the pilot study. Tumour site was chiasmatic/hypothalamic (15), spinal or cervico-medullary region (3), hemispheric (2). 19 patients had received prior chemotherapy and 5 patients had previous radiotherapy. Toxicity was acceptable: 8 patients experienced grade 3-4 ANC toxicity, 1 patient required platelet transfusions, 4 patients RBC transfusion. There were 3 admissions for fever and neutropenia. All patients are evaluable for response. There were 4 partial responses, 3 minor responses, 9 patients had stable disease and 5 showed progression (at 1,1,1,6 and 9 months). 75% patients remained at least stable during the 52 weeks of treatment.

*Conclusion:* Vinblastine shows promising activity in recurrent LGG with a tolerable toxicity profile. The optimal duration of this treatment remains unknown.

## PEDS-3

### Paediatric spinal cord ependymoma (SCE) in the MRI era: A Canadian Paediatric Brain Tumour Consortium Study

*U Dag-Ellams* (Toronto, Ontario); B Wilson (Edmonton, Alberta); P Steinbok (Vancouver, British Columbia); A Carret (Montreal, Quebec); M Silva (Kingston, Ontario); K Aronyk (Edmonton, Alberta); N Laperriere, E Bouffet (Toronto, Ontario)*

Spinal cord ependymoma is rare in the paediatric population. Although the MRI has considerably influenced the management of these tumours, the impact of postoperative management has never been evaluated. Aretrospective review of 18 patients, (11 males, 7 females) paediatric cases of SCE during the MRI scan era was conducted in the CPBTC.

Median age at diagnosis was 11.6 years (1.5-17.4). 16/18 MRI performed was with gadolinium enhancement. Most tumours were located in the lumbar region (12/18), and the median number of segments involved was 4 (2-12). MRI revealed spinal dissemination in 2 patients.

Surgical resection was total in 10 cases, subtotal in 6 and partial in 1, (unknown in one). Postoperatively, 17 MRI were performed. 9 showed no residual disease, 4 residual tumour and 4 equivocal residue. 12/18 spinal cord ependymoma were grade 1/myxo-papillary. Four patients received postoperative radiation for residual tumour. One of these patients received additional chemotherapy. Five patients experienced local relapse. At the last follow-up, all patients were alive. Median follow-up was 2.6 years (0.16-10.16).

*Conclusions:* Myxopapillary ependymomas account for the majority of SCE in the paediatric age. The introduction of MRI in follow-up has enabled decreased use of systematic postoperative radiation.

## PEDS-4

### Intracystic bleomycin therapy forcraniopharyngioma in children: Canadian experience

*J Hukin*, P Steinbok (Vancouver, British Columbia); L Lafay-Cousin (Toronto, Ontario); Y Samson (Quebec, Quebec); W Howes (Halifax, Novia Scotia); E Bouffet (Toronto, Ontario)*

*Introduction:* Surgical removal and radiation therapy is associated with significant morbidity in the pediatric population with craniopharyngioma. The aim of this study was to review the Canadian experience with a less invasive technique, intracystic bleomycin therapy.

*Method:* All centers in the Canadian Pediatric Brain Tumor Consortium were invited to participate in a retrospective review of this treatment. A standardized data form was sent to each center. The data was analyzed in Vancouver.

*Results:* Four centers have participated to date. Bleomycin was considered at each center from 1995, 2000, 2001. 15/17 patients



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with intention to treat, received bleomycin. 10/15 patients had a single cyst. The median size of the largest cyst was 5.8cm (2-8.4). Eleven were treated at diagnosis, four at progression. Median total dose of bleomycin: 55mg (15-115mg). Side-effects: nausea, headache, vomiting. Post bleomycin: vision improvement - four; deterioration in function -2; transient peritumoral edema -1; and morbid obesity and precocious puberty -1. Response to bleomycin: five complete, three partial, five minor and two none. Nine subsequently progressed. Median progression free survival 8mos (4-60), overall survival 6-108mos.

*Conclusion:* Intracystic bleomycin is well-tolerated in children. Bleomycin is a useful option in the treatment of cystic craniopharyngioma in children.

**PEDS-5**

**Treatment failure of intracranial primary germinomas**

*D-S Kim*, T-G Kim, J-U Choi (Seoul, Korea)*

*Purpose:* A radiation dose of 40-50 Gy is able to produce a cure rate in more than 90% of pure intracranial germinomas. However, many attempts have been made to reduce the dose and volume of radiation in hopes of decreasing the toxicity without compromising the disease control rate. In this retrospective study, we examine different radiation doses with cure rate in intracranial germinomas.

*Materials:* We reviewed a series of 117 germinomas diagnosed histologically or clinically between 1979 and 2002 in which there were 10 recurrences. Patients underwent one of three different treatment regimens; radiation alone (N=71), chemotherapy alone (N=9), and combined therapy (N=37).

*Results:* The ten-year overall and relapse-free survival rates were 97% and 93% in radiation alone group, 89% and 67% in chemotherapy alone group, and 92% and 92% in combined therapy group. Radiation therapy and combined therapy were effective in disease control as expected. Tumor recurrence was closely related to the volume but not dose of radiation. Chemotherapy alone showed earlier and higher tumor recurrence rates. In patients that received combination therapy, chemotherapy was useful in reducing the total radiation dose but did have its own toxicity (2 patient deaths)

*Conclusion:* Investigation of further dose reduction seems worthwhile. Radiation therapy alone with less than 40 Gy should be compared with ongoing chemotherapeutic protocols plus low-dose irradiation.

**PEDS-6**

**Pediatric desmoplastic neuroepithelial tumours: clinical presentation and management strategies**

*M Labib*, AJ Sabbagh, J-P Farmer, JL Montes, (Montreal, Quebec);*
*K Meagher-Villemure (Lausanne, Switzerland); S Albrecht, C Bernard (Montreal, Quebec)*

*Background:* Desmoplastic infantile ganglioglioma (DIG), desmoplastic infantile astrocytoma (DIA), and pleomorphic xanthoastrocytoma (PXA) represent a rare group of poorly understood neuroepithelial tumours.

*Methods:* Clinical, imaging and follow-up data were assessed through a retrospective chart review. Eight patients were studied.

*Results:* The median presentation age for DIG/DIAand PXA was 1.75 and 6 years, respectively. One of the DIG patients presented at age of 10. The median follow-up was 8 years. The most common presenting symptom was seizures (50%). Radiologically, most tumors were cystic and enhancing. One tumor occupied the posterior fossa while the rest were hemispheric. Total resection was achieved in 75% of the patients and cured their symptoms. Subtotal resection and conformal radiotherapy prevented the progression of the posterior fossa tumor. Stereotactic biopsy led to an initial diagnosis of high grade astrocytoma in one patient. He received radiotherapy followed by subtotal resection but died 5 years later from malignant desmoplastic noninfantile ganglioglioma.

*Conclusion:* Favorable prognosis is achievable despite aggressive presentation and morphology if these tumors are diagnosed and managed appropriately. DIGs can be infratentorial and may present at older ages. Total surgical resection remains the primary management strategy. Stereotactic biopsy may be misleading.

**PEDS-7**

**A clinico-biological model predicting survival in medulloblastoma**

*A Ray*, M Ho, J Ma, R Parkes, TG Mainprize, J McLaughlin, E Bouffet, JT Rutka, CE Hawkins (Toronto, Ontario)*

*Objective:* To develop a model predictive of outcome for patients with medulloblastoma (MB) based on both clinical and biological markers.

*Methods:* Clinical presentation and survival information was obtained for 120 Hospital for Sick Children patients and a tissue microarray constructed from their tumour samples. The arrays were immunohistochemically assayed for expression of MYC, P53, PDGFR, ErbB2 and TrkC and their ability to predict survival tested.

*Results:* The percentage of immunopositive MBs for each of the markers was as follows: MYC 16%, ErbB2 16%, p53 12%, TrkC 33% and PDGFR 97%. The four strongest predictors of survival based on univariate and multivariate analysis were the presence of metastatic disease at presentation (HR 2.03) and p53 (HR 2.24), TrkC (HR 0.65), and ErbB2 (HR 1.51) immunopositivity. Scaled coefficients were then calculated and a survival estimate determined based on the sum of the coefficients for the markers present in a particular tumour.

*Conclusions:* We present one of the largest single institution studies of pediatric MB and the first attempt at combining both clinical and biological markers to stratify MB patients into risk groups. Further, the fact that the biological markers studied are all immunohistochemistry-based makes this method widely applicable throughout the world.

**PEDS-8**

**Verotoxin and the treatment of medulloblastoma**

*F Rutten*, B Salhia, JTRutka, CA Lingwood (Toronto, Ontario)*

Medulloblastomas (MB) are highly malignant tumors representing the most common malignant posterior fossa tumor in childhood. Only 60% of children have a 5-year disease free survival after therapy.

Verotoxin1 (VT1) is an *Escherichia coli* toxin that has been proposed as a novel anti-neoplastic treatment in several human



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cancers including those of bladder and ovarian origin, myelomas, lymphomas, astrocytomas and meningiomas. The actions of VT1 are mediated through its glycolipid receptor, globotriaosylceramide ($Gb_3$).

We investigated the effects of VT1 *in vitro* on different MB cell lines: UW228, UW426, ONS76, TE671 and DAOY. After treatment with VT1, only the UW228 cell line was sensitive to VT1-cytotoxicity as demonstrated by cell viability assays. $Gb_3$ status was determined through glycolipid extraction followed by thin layer chromoaography and VT1 overlay binding studies. These data showed the presence of $Gb_3$ and VT1 binding in the UW228 cell line.

In order to determine the clinical significance of our study, co-immunostaining of human MB samples for $Gb_3$ and Factor VIII demonstrated co-localization of $Gb_3$ and Factor VIII to the micro-vascular endothelial cells of the tumors.

Future studies in animals will help us to determine the therapeutic potential of VT1 in the management of human MB.

**PEDS-9**

**Surgery for brainstem tumors with the assistance of multimodality intraoperative neurophysiological monitoring: Early neurological outcome in 37 patients**

*F Sala*, P Lanteri, B Masotto, A Bricolo (Verona, Italy)*

*Purpose:* We assessed the reliability of intraoperative neurophysiological techniques to prevent injury to brainstem motor pathways and cranial nerves motor nuclei during surgery.

*Material and Methods:* Thirty-seven brainstem tumor patients were studied since 2001. Mapping of the floor of the fourth ventricle or of the cerebral peduncle was used to enter the brainstem avoiding injury to cranial motor nerve nuclei (VII,XI/X,XII) and corticospinal tracts. We continuously monitored: 1) transcranially elicited muscle motor evoked potentials (mMEPs) from upper and/or lower limbs; 2) transcranially elicited corticobulbar mMEPs and 3) spontaneous EMG activity from muscles innervated by cranial motor nerves (VII,XI/X,XII). For mMEPs, absence/presence criteria were used to predict outcome. Correlations between neurophysiological events and postoperative outcome were assessed as false positive (FP), false negative (FN), true positive (TP) and true negative (TN) results.

*Results:* Surgical removal was total (100%) in 22 cases, near total (90%) in 10, subtotal (<90%) in 5. Mapping was successful in all cases. 1-2) Limb/corticobulbar mMEPs were specific and sensitive in all cases. Surgery was abandoned in two cases because of transient or permanent mMEP loss, this latter resulting in a worse postoperative motor deficit. 3) Spontaneous EMG activity showed 8 FP and 5 FN results. Postoperatively, no patient required tracheostomy or percutaneous endoscopic gastrostomy.

*Conclusions:* In most of the patients neurophysiological mapping/monitoring prevented permanent injury to corticospinal/ corticobulbar tracts and motor nuclei during surgical manipulation of the brainstem. However, neurophysiological methods cannot yet completely prevent injury to complex reflexes such as swallowing and coughing.

**PEDS-10**

**Medulloblastoma in the second decade of life: A specific group with respect to toxicity and management. A Canadian Paediatric Brain Tumor Consortium Study**

*U Tabori* (Toronto, Ontario); J Hukin (Vancouver, British Columbia), B Crooks (Halifax, Nova Scotia); N Laperriere (Toronto, Ontario); AS Carret (Montreal, Quebec); D Strother (Calgary, Alberta); M Silva (Kingston, Ontario); D Eisenstat (Winnipeg, Manitoba); B Wilson (Edmonton, Alberta); I Odame (Hamilton, Ontario); C Mpofu (Saskatoon, Saskatchewan); Y Samson (Quebec City, Quebec); LSung, E Bouffet (Toronto, Ontario)*

*Background:* 25% of patients diagnosed with medulloblastoma are >10 year-old at presentation. Chemo-radiotherapy protocols have been shown to be exceedingly toxic in adults. The magnitude of the problem in teenagers is unknown.

*Methods:* We retrospectively studied the toxicity and outcome of children aged 10-20 years with medulloblastoma, treated at centers of the CPBTC between 1986-2003. Detailed data from 2 chemotherapy protocols (ICE-ifosfamide-carboplatin-etoposide and CCV-CCNU-cisplatin-vincristine) were collected for teenagers and compared to controls aged 5-10 years.

*Results:* A total of 63 patients were analyzed. Grade >2 ototoxicity, neurotoxicity and grade 3-4 hematotoxicty occurred in 46%, 78% and 95% of chemotherapy treated patients, respectively. Toxicity resulted in treatment delay, dose-modification or protocol-discontinuation in 68%, 74% and 19% of cases, respectively .

Teenagers on ICE and CCV protocols had significantly more hematotoxicity ($P<0.0001$) and neurotoxicity ($P=0.0017$) than controls. In both protocols, toxicity resulted in more treatment delays ($P<0.0001$) and dose modifications ($P=0.0073$) in teenagers than controls.

Five year overall and event free survival were 79±6% and 70±6% respectively with a median time to relapse of 2.9(0-8.4) years.

*Conclusions:* Most teenagers with medulloblastoma cannot tolerate current standard chemo-radiotherapy strategies. Time to relapse was longer than reported in pediatric series. This age group may necessitate different approach than younger children.

**PEDS-11**

**Telomere erosion and lack of telomerase activity affect the biological behavior of pediatric low grade gliomas**

*U Tabori*, B Vukovic, M Zielenska, C Hawkins, J Rutka, E Bouffet, J Squire, D Malkin (Toronto, Ontario)*

*Background:* One of the most striking characteristics of pediatric low grade gliomas (PLGG) is their tendency to cease growing, and in rare cases to spontaneously regress. A plausible biological mechanism has not yet been demonstrated to explain this phenomenon. We hypothesized that growth arrest of PLGG may be related to telomere maintenance and dysfunction.

*Methods:* Telomerase activity was measured using PCR-ELISA assay in 11 primary PLGGs. To determine whether there was an alteration in telomere length, 10 paraffin-embedded samples from 5 recurrent/progressive PLGGs (2 samples from each patient at diagnosis and progression, respectively) were investigated using quantitative nucleic acid (PNA) FISH analysis.



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*Results:* None of the 11 PLGGs demonstrated telomerase activity, as opposed to most of the high grade pediatric CNS tumors. For each of the 5 paired cases, a significant reduction in telomere length was detected in the second surgery sample compared to the diagnostic one ($p<0.0001$). Furthermore, increased aneusomy was encountered in 4 of the 5 cases suggesting that telomere shortening is associated with tumor progression.

*Conclusions:* These findings support the hypothesis that telomere erosion and lack of telomerase activity may be involved in the tendency of PLGGs to undergo growth arrest or spontaneous regression.

# QUALITY OF LIFE / EPIDEMIOLOGY

## QOL-1

### Ethical issues in clinical neuro-oncology trials

*M Bernstein* (Toronto, Ontario)*

Clinical research with patients is a moral and scientific imperative to help determine the most beneficial, safest, and most cost-effective treatments for patients with brain tumours. Besides medical and scientific issues, there are numerous ethical issues concerning the conduct of clinical research.

Some obvious ones known to most investigators include: the need for Research Ethics Board approval; the need for informed consent; is there any financial conflict of interest; what is the harm/benefit ratio and specifically is the perceived harm of the experimental treatment acceptable; is there a placebo and if so is it ethical; and others.

Some more subtle ones include: is there any nonfinancial conflict of interest and, specifically, is it ethical for the investigator and the care provider to be one and the same; is it ethical to pay research subjects; what should we do when a patient's desires are in opposition to the terms of a study; was a clinically meaningful effect sought as opposed to simply a statistically significant one; and others.

The author will discuss these issues using examples. A novel framework for evaluating the bioethical acceptability of a clinical trial will be presented.

## QOL-2

### Reasons for poor accrual in a quality of life study involving patients with brain metastases

*N Bradley *, E Sinclair, L Holden, E Chow, G Chan, V Yau, C Danjoux, E Barnes, C Hayter, M Tsao (Toronto, Ontario)*

*Objective:* To examine accrual rates and reasons for nonaccrual into a quality of life (QOL) study for patients with brain metastases (BrM).

*Materials/Methods:* The inclusion criteria for this study were: a diagnosis of BrM; daily dexamethasone dose of 12-16 mg for at least 48 hours before the first QOLassessment; a mini-mental status exam score of at least 25/30, ability to read and understand English and the presence of a proxy. The FACT-Br QOL questionnaire was administered to the patient and proxy at the time of referral, and at one and two months following radiotherapy.

*Results:* Sixty patients with BrM were seen from 5/12/03 to 11/24/03. During this time, 9 patients (15 %) agreed to participate in the study. Thirty-two patients (55 %) did not meet inclusion criteria, 12 (20 %) declined and 8 (13.3 %) were considered unsuitable by the Radiation Oncologist.

When the option of telephone or mail follow-up was offered, accrual rates increased from 8.3% (5/12/03 to 8/4/03) to 19.4% (8/4/03 to 11/24/03).

*Conclusions:* Eligibility criteria should be as broad as possible. The burden on patients to provide follow-up data should be minimized. This can be achieved by offering mail or telephone follow-up rather than clinic visits.

## QOL-3

### Quality of life analysis in patients with anterior skull base neoplasms

*J Irish, C Palme, M Katz, DH Brown*, R Gilbert, F Gentili, P Gullane (Toronto, Ontario)*

*Introduction:* The aim of this paper is to describe quality of life (QOL) outcomes using contemporary, validated QOLinstruments in patients treated for anterior skull base neoplasms.

*Methods and Materials:* We identified 47 patients alive after treatment. Patient self-assessment using standard QOL demiologic Studies Depression Scale (CES-D), and Atkinson Life Happiness Rating (ALHR), was carried out. In addition, we measured functional outcome using our own Midface Dysfunction Scale.

*Results:* A response rate of 76% (35/47) was achieved. Tumor removal was achieved via a transfacial and/or craniotomy approach in all patients. Adjuvant radiotherapy was required in 16 patients. Complications were experienced in 6/27 patients (22%). The median total FACT score was 118±21 (range, 63 to 141), the median ALHR was 9 ± (range, 6 to 11), and the median CES-D was 17 ± (range, 9 to 46). Significant disturbance of smell and nasal crusting was reported by 69% and 61%, respectively. CES-D score > 16/16 and patients with recurrent disease correlated with a lower FACT score ($p = 0.02, 0.002$, respectively). Adjuvant radiotherapy correlated with a lower score in the FACT Head and Neck subscale ($p = 0.05$). Gender, marital status, tumor pathology, surgical approach, reconstruction, or rate of complications did not predict a worse QOL.

*Conclusion:* Patients who survive anterior skull base tumors have an overall acceptable QOL. The most common complaints relate to disturbance of midface function. The QOLoutcomes in this group of patients would continue to support aggressive clinical interventions for long-term survival.

## QOL-4

### Outcome of treatment induced high-grade glioma (HGG) in children: A study of the Canadian Pediatric Brain Tumour Consortium (CPBTC)

*AS Carret* (Montreal, Quebec); U Tabori (Toronto, Ontario); B Crooks (Halifax, Nova Scotia); J Hukin (Vancouver, British Columbia); I Odame (Hamilton, Ontario); DLJohnston, DL Keene (Ottawa, Ontario); C Freeman (Montreal, Quebec); E Bouffet (Toronto, Ontario)*

Children treated for cancer are at risk for long-term toxicities including second malignancies. Reports on treatment induced-HGG



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in survivors of childhood cancers are scarce. We report treatment related-HGG in 16 children who were treated with irradiation ± chemotherapy for either acute lymphoblastic leukemia (n=7) or solid tumour (n=9).

Median age at cranial radiation was 4.5 yrs (range, 0.5-9). Median age at HHG diagnosis was 14.5 yrs (range, 7-19) with a median interval between radiation therapy and HGG diagnosis of 8 yrs (range, 6-14). All gliomas occurred within the previous radiation fields. Fifteen patients had a biopsy with histology consistent with glioblastoma multiforme (n=13), anaplastic astrocytoma (n=1), gliomatosis cerebri (n=1), gliosarcoma (n=1). For one patient the diagnosis was based on imaging only. Twelve patients received chemotherapy and 2 patients palliative treatment only. Surgical resection was part of the treatment for 9 patients including 2 gross complete resections. Six patients were re-irradiated. The overall median survival for all the patients was 8 months (range, 0.1-82 months).

High-grade glioma may occur in children as a consequence of therapy for a prior malignancy. Cranial radiation therapy should be considered as a risk factor. The role of surgery and re-irradiation is still not clear and would require a larger epidemiological study.

## QOL-5

### An educational program for the caregivers of persons diagnosed with brain tumours

*R Cashman*, L Bernstein, D Bilodeau, G Bovett, B Jackson, M Yousefi, J Perry (Toronto, Ontario)*

*Background:* Providing care for persons diagnosed with brain tumours is a formidable responsibility for family members. The dismal prognosis, side effects of treatments, and changes in brain function, personality and behaviour pose unique challenges in care provision.

*Purpose:* To evaluate the impact of providing information to caregivers of patients afflicted with brain tumours.

*Methods and Results:* A structured educational program for the caregivers of brain tumour patients was developed based upon multidisciplinary expert opinion and caregiver review. Using a multiple choice test format, knowledge is assessed before, immediately following, and one month following the program. Open-ended questions explore the specific hardships associated with caregiving, as well as additional benefits derived from the program.

To date, one session has been held and was attended by thirteen caregivers; a second will be completed prior to the CNO meeting. The preliminary sample revealed marked improvement in test scores immediately after the program, demonstrating effectiveness of knowledge transfer. Scores remained statistically significantly improved one month following program participation, demonstrating long-term retention of the test material. Specific quantitative and qualitative data will be presented and serve as a basis for understanding caregivers'needs and experiences.

Supported through the Crolla Family Brain Tumour Research Unit and a Practice-Based Research Award, Sunnybrook & Women's College Health Sciences Centre.

## QOL-6

### Longterm follow-up of an anaplastic oligodendroglioma and mixed glioma population

*BJ Fisher*, DR Macdonald, GS Bauman (London, Ontario)*

One hundred and three patients with a diagnosis of anaplastic oligodendroglioma (75) or mixed oligoastrocytoma (28) were referred to the London Regional Cancer Centre between 1985-2001. Median age was 43 years, 79% were under age 60 years at time of presentation. Sixteen patients had a prior diagnosis of low-grade glioma. Presenting CT/MRI scans reported necrosis in 35%, calcification in 35% and enhancement in 74% of tumours. Twenty-one of these patients underwent gross total resections of their tumours confirmed by postoperative imaging. The remainder underwent biopsies or subtotal resections. Twenty-seven patients received 1-8 doses of chemotherapy as an initial treatment. The most common regimen was procarbazine, vincristine and CCNU. Of these 27 patients, 3 attained a complete response, 4 a partial response, 1 stable disease, 19 no response or progression. Eighty-four patients received radiotherapy, 14 with additional concurrent chemotherapy. Forty-seven had stable or responsive tumours, 17 progressed. Additional postradiation chemotherapy was administered to 46 patients with subsequent radiological improvement in 15, stable disease in 11 and progression in 9. Overall median time to progression was 20 months and median overall survival was 34 months. Subgroup analyses will be presented.

## QOL-7

### Sex steroid hormone exposures and risk for anaplastic astrocytoma and glioblastoma multiforme

*BS Jhawar* (Toronto, Ontario); CS Fuchs, GA Colditz, MJ Stampfer (Boston, Massachusetts)*

To investigate the risk of pathologically confirmed astrocytoma in relation to sex-hormone exposures, we prospectively analyzed a cohort of 121,700 female nurses.

During 1,188,810 person-years of follow-up, 121 cases were confirmed. After adjusting for age, compared to postmenopausal women who had never used postmenopausal hormones, the relative risk (RR) for premenopausal women was 0.63 (95%CI=0.30–1.33). When we additionally adjusted for other covariates we found increased risk for postmenopausal women who were past hormone users (duration <2.5 years, RR=1.59, (95%CI=0.81–3.10); duration >2.5 years, RR=1.95, (95%CI=1.02–3.75), and no significant association for current users (RR=1.26, 95%CI=0.72–2.21). There was no association for the past use of oral contraceptive (RR=0.74, 95%CI=0.47–1.18). The risk for astrocytoma also decreased with increasing age at menopause (RR=0.97, p=0.03). In multivariate models, for age at menarche we found that compared with women whose menarche occurred before age 12, the RR for women with menarche at ages 12–14 was 1.20 (95%CI=0.78–1.85) and after age 14, the RR was 1.84 (95%CI=0.98-3.44). We observed a tendency for lower risk among parous women compared to nulliparous women (RR=0.61, 95%CI=0.32–1.14). When we limited the analysis to cases of glioblastoma multiforme, we found all the preceding associations to be stronger. No meaningful associations were found for anaplastic astrocytoma risk.

Our prospective data support a modest role of sex hormones in



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the growth of astrocytoma. The findings compliment previous work that has documented functional sex-hormone receptors on many of these tumours.

**QOL-8**

**Concurrence of glioma and multiple sclerosis**

*S Khan (Saskatoon, Saskatchewan); J Buwembo*, Q Li (Regina, Saskatchewan)*

*Objective:* Concurrence of multiple sclerosis (MS) and glioma is extremely rare. Correct diagnosis of the two entities remains essential, as they are treated differently. We report a case with such a presentation.

*Clinical Presentation:* A 29-year-old Caucasian female diagnosed with MS for 7 years, presented with a history of headaches and a single episode of new onset seizures. Her physical examination was unremarkable and she was placed on anti-epileptics. A CT scan showed a large right frontal brain lesion, causing minimal mass effect. MRI revealed this lesion to be nonenhancing, accompanied by numerous smaller lesions resembling MS plaques. It was unclear whether the large frontal lesion was a demyelinating MS plaque, or an intra-axial tumour.

*Intervention:* A stereotactic-guided biopsy was performed, targeting the right frontal lesion. The resultant tissue specimen was diagnostic of a glioma. The patient underwent an elective, frameless, stereotactic-guided craniotomy to effect gross total resection.

*Conclusion:* Final pathology was consistent with an oligoastrocytoma (WHO grade II). Postoperatively, the patient remained neurologically intact. She was discharged home with plans for observation and serial MRI examinations. We demonstrate the importance of rigorously investigating uncharacteristic lesions in patients with MS.

**QOL-9**

**Infant medulloblastoma: Review of an institutional experience**

*L Lafay-Cousin*, E Bouffet, D Mabbott, U Dag-Ellams (Toronto, Ontario); D Hargrave (London, United Kingdom); D Hyder, A Huang (Toronto, Ontario)*

A retrospective review of 33 patients diagnosed at less than 3 yrs of age with medulloblastoma was conducted to assess for potential prognosticators in this high risk group. At diagnosis, median age was 1.8 yrs; 55% were metastatic. 28/33 patients received adjuvant therapy after surgery. 21/28 received chemotherapy up front, with the aim of deferring or eliminating radiation. 76% (16/21) progressed (median of 9.9 months from diagnosis); 33% (2/6) had radiation salvage; 3/21 achieved prolonged remission with chemotherapy. 7/21 patients received chemotherapy with early radiation; 71% (5/7) were alive (median 116 month follow-up). Overall survival for all treated was 35%; 5 year EFS and OS were 23.4% and 23.7% respectively. Outcome did not correlate with metastatic status; extent of surgical resection correlated with better outcome in patients without metastases (p=0.043). Of 10 survivors; 50% (5/10) received early radiation; 20% (2/10) had radiation salvage, 30% (3/10) were cured with chemotherapy alone. Follow-up neurocognitive assessment in 6/10 survivors (median time 2.9 yrs) showed significant IQ decline associated with craniospinal irradiation. In summary, infant medulloblastoma are curable with radiation but with substantial neurocognitive sequelae. Some infant medulloblastoma are curable without radiotherapy, future biologic studies should lend valuable insights into this unique sub-group.

**QOL-10**

**Characterization of brain tumour-associated headaches pre- and post-neurosurgical intervention**

*B Lo*, K Reddy, R Hollenberg (Hamilton, Ontario)*

*Background:* Contrary to the long-established dogma that increased intracranial pressure causes severe morning headaches in those with brain tumours, this belief may not be always valid. Thus, a study was conducted to better define the incidence and character of brain tumour-associated headaches.

*Methods:* This retrospective, observational study sampled 151 patients from Hamilton Health Services, from January 1 to August 15, 2003.

*Results:* Mean age of patients: 56.9. 79% had primary tumour. 38% were gliomas, 25% were meningiomas. Presenting symptoms: headaches (35%), seizures (23%), weakness (25%), gait ataxia (26%), changes in level of consciousness (21%), visual disturbance (14%). 53 of 151 patients had headaches (35%). Of those with headaches, 21 had a triad of headache, vomiting and visual disturbance (40%); 9 had morning headaches (17%); 21 had constant, severe headaches (40%). Half of the brain tumour-associated headaches were of a nondescript quality. Other qualities: sharp (13%), dull (3%), deep (13%), pulsatile (8%), nonthrobbing (13%). Mean transverse diameter of brain tumours: 4.3 cm in those with headaches, 3.5 cm in those without headaches ($t = 2.69$, $p = 0.004$). Postoperatively, 70% of brain tumour-associated headaches improved to occasional to no headaches.

*Conclusions:* Only 1/3 of brain tumour patients had headaches. Of those with brain tumour-associated headaches, only a small proportion had morning headaches. Size of brain tumour has a statistically significant relationship with occurrence of headaches. Majority of headaches improved postoperatively.

**QOL-11**

**Academic and behavioral outcome following treatment with cranial radiation in childhood**

*D Mabbott*, B Spiegler, M Greenberg, J Rutka, D Hyder, E Bouffet (Toronto, Ontario)*

*Purpose:* Treatment with cranial-spinal radiation for malignant posterior fossa (PF) tumors is consistently associated with a progressive decline in intelligence but its impact on academics and behavior has received little attention. We examine patterns of change over time in these under studied areas.

*Patients:* Thirty-one children with PF tumors (27 medulloblastoma; 4 ependymoma) were followed with serial evaluation of academics and/or behavioral functioning. Patients were treated with standard (18 with 3400-3600 cGy) or reduced (12 with 2340 – 3020) dose cranial-spinal radiation and a boost to the PF. One patient was treated with PF radiation only. The rate of change in test scores was determined using a mixed model regression.

*Results:* Spelling and mathematics achievement declined over time (slopes > -1.21, ps < .01) as did parent/teacher ratings of



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academic ability (slopes > -.93, ps < .01). Reading was a stable deficit. Based on parent/teacher ratings, increases in social difficulties, social withdrawal, and attention problems (slopes <1.06, ps <.05) were observed. Cranial radiation is associated with declines in academic ability, and increases in social and attention problems. However, psychological distress was not evident, highlighting the resiliency of children and families in the context of severe medical stressors.

**QOL-12**

**Neurocognitive status in children after treatment of tumours in the region of the third ventricle**

*D Mabbott*, S Guger, K Kennedy, E Bouffet, B Spiegler (Toronto, Ontario)*

*Purpose:* Central tumors (pineal or suprasellar/pituitary region) are relatively infrequent but may have an impact on behavior and cognition. We explore neurocognitive and behavioral outcome for this population.

*Methods:* Retrospective chart review was conducted for 12 patients (7 germinona, 3 mixed germ cell, 1 pineocytoma, 1 teratoma; mean age at diagnosis = 10.37 years) seen for neurocognitive evaluation. Treatment involved surgery (6 biopsy, 4 subtotal), shunt insertion (5 patients), chemotherapy (11 patients) and either focal or cranial radiation (7 and 5 patients, respectively). Neuropsychological assessment was conducted an average of 3.13 years following radiation (mean age at assessment =13.78 years).

*Results:* IQ (FIQ = 98) language, spelling, reading, mathematics, visual-perceptual ability, and executive functioning were intact but speeded sequencing was poor. Poorer attention was observed for patients treated with cranial-spinal compared to focal radiation. Posterior central tumors were associated with memory impairments relative to anterior tumors (mean SS = 76 versus 103). Concerns regarding somatic difficulties and social problems were elevated for anterior tumours, however. Two patients with tumors extending across anterior and posterior locations did poorest on all measures. Based on these preliminary data, tumor location appears most important in understanding neurocognitive and behavioral outcome in children treated for central tumors.

**QOL-13**

**End-of-life care of children with central nervous system (CNS) tumours**

*P McGee*, E Bouffet (Toronto, Ontario); R Sinah, M Breen, D Hargrave (London, United Kingdom)*

*Purpose:* This study examined the end-of-life care provided to children dying of a CNS tumour in two different oncology programs in two different countries.

*Methodology:* A retrospective analysis was performed to describe each child's clinical course and the care provided by members of each oncology team.

*Results:* The study included 102 children who died of a CNS tumour between January 1, 1997 (London)/January 1, 2001 (Toronto) and December 31, 2003. Twenty-eight percent of the children were diagnosed with diffuse pontine glioma, 24% with medulloblastoma/PNET, 20% with high-grade glioma, 11% with ependymoma, and 17% with other tumour types. The average age at diagnosis and death was 6.9 years and 8.1 years respectively. The mean times from diagnosis and tumour progression to death were 15.1 months and 4.1 months respectively. Overall, 53% of children died at home (60% London; 46% Toronto). Symptoms managed included: pain (60.5%), immobility (57%), seizures (46%), swallowing difficulties (36%), and impaired speech (32%). The commonest interventions were: dexamethasone (70%), opiate analgesia (55%), anticonvulsants (48%), and nasogastric tube (28%).

*Conclusion:* Few studies have specifically attempted to describe the dying trajectory of children with a CNS tumour. This study elucidates issues related to end-of-life care for children with CNS tumours.

# RADIATION

**RAD-1**

**Delayed postoperative radiation treatment in pituitary adenoma: Its impact on long-term tumorcontrol**

*O Agboola*, A Modha, B Benoit, A Girard, S Dahrouge (Ottawa, Ontario); R Donker (Utrecht, Netherland)*

*Purpose:* To determine the impact of withholding postoperative radiation treatment (RT) for incompletely resected pituitary adenoma (PA), on tumor recurrence, the overall progression free survival (PFS) and survival.

*Methods and Materials:* We studied two groups of patients with PA (169 cases) drawn from the same population base over the same time period (1983 - 1997). The two groups (SR and S) had surgery as initial treatment. The SR group (48 cases) received postoperative RT for incompletely resected tumors and or persistently elevated hormone levels. The S group, (121 cases) received RT± second surgery after first recurrence.

We compared the PFS in each group from initial treatment to first recurrence. To determine the impact of delayed RT, we compared the time to progression between initial treatment and first recurrence for the SR group with progression following radiotherapy after first recurrence in the S group.

*Results:* The PFS from initial treatment to first recurrence was significantly better in the SR group (p<0.0001). The 5 and 10 years PFS in the S group (94% and 82%) was comparable to PFS (95% and 83%) in the SR group (p=0.88). Overall survival was not significantly different between the two groups (p=0.44).

*Conclusion:* Postoperative RT significantly decreases the probability of recurrence following incomplete surgical resection. Delaying radiotherapy to the time of recurrence does not negatively impact overall tumor control.

**RAD-2**

**Helical tomotherapy for brain tumors: A planning comparison**

*S Yartsev, T Kron, (London, Ontario); L Cozzi, A Fogliata (Bellinzona, Switzerland); G Bauman* (London, Ontario)*

Helical tomotherapy (HT) is a novel radiotherapy treatment delivery method based on the continuous rotation of an intensity modulated fan beam around a patient slowly advancing through a



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ring gantry. Radiotherapy plans based on HT delivery were evaluated in comparison with plans previously obtained for the same patients using 3D conformal radiotherapy (3DCRT), stereotactic arc therapy (SRS/T), intensity-modulated radiotherapy with photons (IMRT), and radiotherapy with protons (spot scanning and passive scanning)(Bolsi A, Fogliata A, Cozzi L. Radiother Oncol 2003;68:1-14). HT plans for five acoustic neurinomas, five meningiomas, and two pituitary adenomas were computed using an helical tomotherapy inverse treatment planning system (TomoTherapy Inc. Madison). Dose-volume histograms and dose metrics were used to compare HT to the other planning techniques. Helical tomography was shown to be able to produce significantly better target dose uniformity and conformity even compared to proton radiotherapy, while keeping irradiation of organs at risk to a level comparable to the other photon techniques. Tomotherapy was found to be especially useful in the cases when tumour was situated in close vicinity of several OARs making it difficult to treat with conventional techniques.

**RAD-3**

**Degradation of the catalytic subunit of DNA-dependent protein kinase by a herpes simplex virus vector enhances the radiosensitivity of human glioblastoma cells**

*CG Hadjipanayis*, NA DeLuca (Pittsburgh, Pennsylvania)*

The herpes simplex virus (HSV) immediate-early (IE) protein, ICP0, has been shown to induce the degradation of the catalytic subunit of DNA-dependent protein kinase (DNA-PKcs), a key player in the repair of DNA double-strand breaks (DSBs) produced by ionizing radiation (IR).

Two HSV-1 vectors were used to infect radioresistant T98 and U87-MG human GBM cells. The HSV-1 vector, d106, solely expresses ICP0 while d109 is defective for all IE proteins. After cell infection (MOI of 10 PFU/cell) for 24 h, cells were treated with escalating single doses of IR (0, 5, 10, and 20 Gy). Cell viability and proliferation after IR treatment were assessed with an MTT cell proliferation assay at 0, 2, 4, and 6 days. Cells infected with d106 showed a dose-dependent decrease in cell survival and proliferation after IR treatment compared to d109 and mock infected cells. An adenovirus, which expresses ICP0, confirmed the decrease in U87-MG survival after infection and IR treatment. Clonogenic survival assays revealed a low surviving fraction of U87-MG cells after d106 infection and IR treatment (.001).

Western blot analysis showed DNA-PKcs degradation at 24 hours after d106 infection in both cell lines. Indirect immuno-fluorescence revealed persistent DNA DSBs, or gH2AX foci, in irradiated U87-MG cells infected with d106. Apoptosis was determined to be the mode of cell death in T98 cells after d106 infection and irradiation as levels of cleaved, caspase-3 were detected.

**RAD-4**

**Gamma knife radiosurgery for benign cavernous sinus tumors: Quantitative analysis of treatment outcomes**

*J S Kuo* (Toronto, Ontario); JCT Chen, C Yu, V Zelman, SL Giannotta, Z Petrovich, MLJ Apuzzo (Los Angeles, California)*

*Objective:* Analysis of factors related to treatment outcomes in gamma knife radiosurgery (GKRS) of benign cavernous sinus tumors.

*Methods:* From 1994-2002, 133 patients with 57 meningiomas and 76 pituitary tumors (49 nonfunctional adenomas, 15 prolactinomas, 5 ACTH-secreting tumors, 6 GH-secreting tumors, 1 pluri-hormone-secreting tumor) were treated. Median tumor volume was 3.4cm$^3$ and median prescribed dose was 15 Gy to the 50% isodose line.

*Results:* Among 133 treated tumors, 97.8% were controlled with low morbidity at 3.5 years median follow-up. For meningiomas, 51% were unchanged and 46% were smaller after 15.2 months. For pituitary tumors, 66% were unchanged and 33% were smaller after 21 months. Cranial nerve function improvement occurred in 36.5%, while 2% developed new deficits. Endocrine function was normalized for all patients with GH-secreting tumors, 4 of 5 ACTH-secreting tumors, and 13 of 15 prolactinomas within 2 years. Additional external beam radiotherapy is associated with a significantly higher incidence of radiation-induced injury: 29.4% of patients who received GKRS and radiotherapy versus 0.8% of patients who only had GKRS. Quantitative analysis revealed that under-dosed tumor volume and total tumor volume correlated well with treatment outcomes.

*Conclusions:* GKRS is safe and highly effective for treating cavernous sinus tumors, but continued analysis of treated patients is needed to evaluate long term disease control and potential late complications.

**RAD-5**

**Metronomic photodynamic therapy using 5-aminolevulinic acid induced protoporphyrin IX in a rabbit brain tumormodel**

*A Bogaards, A Varma, SK Bisland, L Lilge, PJ Muller*, BC Wilson (Toronto, Ontario)*

*Background:* Clinical investigations of fluorescence-guided resection (FGR) and photodynamic therapy (PDT) are ongoing in brain tumor patients. Anew application, metronomic PDT, (mPDT) consists of a continuous light illumination of photosensitized tissue and has been shown to induce apoptosis. We investigated the preclinical feasibility of FGR followed by mPDTin order to delay tumor regrowth and improve survival.

*Methods:* 18 rabbits with VX2 tumors were divided in 3 groups, A: no FGR – no mPDT, B: FGR – no mPDT and C: FGR + mPDT. mPDTwas delivered using intracranial LED implants and automatic timer switch and battery in a backpack. Animals were sacrificed upon first signs of neurological defect. H&E, Gram and TUNEL stains were performed on brain sections to investigate, tissue morphology, bacteriological infection and PDT-induced apoptosis, respectively.

*Results:* A survival increase was found performing FGR vs. no surgery. As a result of mPDT, tumor selective mPDT induced apoptosis was demonstrated, indicating the potential of this treatment strategy. No infectious complication occurred.

*Conclusion:* These initial results indicate the technical and surgical feasibility of FGR followed by mPDT. Further investigation is required to find optimum mPDT parameters that may lead to sufficient tumor cell death and thus improved survival.



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**RAD-6**

**Preliminary survival results of a randomized controlled clinical trial of photodynamic therapy [PDT] in the treatment of newly diagnosed malignant gliomas using porfimer sodium [Photofrin]**

*P Muller*, B Wilson, L Lilge, A Varma, A Bogaars (Toronto, Ontario); F Hetzel, Q Chen, T Fullagar (Denver, Colorado); J Abrams (Detroit, Michigan)*

*Background and Objective:* Our prospective trial of PDT in newly diagnosed malignant gliomas has recently closed. [NIH 5PO1CAS043892-13]

*Methods:* Patients were randomly assigned to the control [surgical resection + postoperative radiotherapy + chemotherapy] or to the experimental arm [surgical resection + intraoperative PDT + postoperative radiotherapy + chemotherapy]. The PDTarm received 2 mg/kg Photofrin iv 12-36 hours prior to resection and 110-130 J/cm$^2$ photo-illumination]. A total of 101 participants have been enrolled [47 at Toronto and 54 at Denver]. A total of 77 individuals, 39 from Toronto and 38 from Denver met the eligibility criteria and accepted their assigned treatment. Patients with pathologically confirmed glioblastoma multiforme are included in this study cohort.

*Results:* No clinically or statistically significant differences in demographic characteristics or baseline neurological measures between treatment arms were identified. The median survival was 8 mos. (95% C.I. 3 mos., 10 mos.) for patients receiving surgery alone and 11 months (95% C.I. 6 mos., 14 mos.) for patients on the PDT+surgery arm. The curves crossed at approximately 15 months.

*Conclusions:* The median survival of patients with GBM was extended by 3 months in the PDT arm. The preliminary analysis of the primary end-point [crude survival] has not reached statistical significance.

**RAD-7**

**Stereotactic and image-guided hypofractionated intensity modulated radiotherapy (IMRT) for previously irradiated epidural paraspinal metastatic tumors**

*Y Yamada*, M Lovelock, K Yenice, M Bilsky, J Zatcky, S Leibel (New York, New York)*

*Purpose:* Epidural metastatic spinal lesions which recur after surgical, radiation and systemic management often present vexing clinical scenarios. The results of repeat radiotherapy utilizing IMRT with precise noninvasive immobilization of the spine utilizing stereotactic and image guided target localization are presented.

*Methods and Materials:* Twenty-two patients with recurrent metastatic epidural disease underwent repeat radiotherapy after prior therapy with surgery, conventional palliative radiotherapy and systemic therapy. These patients were treated with IMRT immobilized in a relocatable stereotactic body frame or body cradle designed for image guided radiotherapy. The median dose to the target volume was 2000cGy/5 fractions. All patients were followed with regular MRI evaluation q3-4 months.

*Results:* The median follow-up is 9 months (2-22 months) and 95% of patients reported significant durable palliation of presenting complaints. Two patients had radiographic evidence of disease progression (mean time to failure = 5.5 months). Actuarial local control was found to be 81%. No patients have experienced significant toxicity.

*Conclusion:* The marriage of IMRT and noninvasive spinal immobilization have made repeat radiotherapy for recurrent epidural lesions feasible. Almost all patients have experienced reduction in symptoms and no serious toxicity has been encountered. Although preliminary, the results are encouraging.

**RAD-8**

**Small series of radiation-induced peripheral nerve tumors and review of the literature**

*G Zadeh*, P Shannon, S Wong, A Guha (Toronto, Ontario)*

Tumors of the peripheral nerves, both malignant and benign, are rare reported complications of radiation therapy. We identified four cases of radiation-induced peripheral nerve tumors in our practice, which had fulfilled Cahans criteria for radiation-induced tumors. An example is a non-Neurofibromatosis (NF1 or NF2) male presenting with an enlarging neurofibroma of the brachial plexus, 20 years after radiation therapy to the region for Hodgkins lymphoma. The pathology, similar to the other three cases, demonstrated a moderate degree of nuclear atypia, hypercellularity, and a high proliferative index. These features were indicative of increased aggressiveness, compared to NF1 or spontaneous benign neurofibromas.

These cases illustrate that radiation is a potential carcinogen to peripheral nerves, a well-recognized long-term complication after radiation to the central nervous system. Focused radiation is being increasingly advocated as primary treatment of benign vestibular schwannomas, even in young patients and those with germline predisposition syndromes such as NF2. Since peripheral and cranial nerves, such as those in the cerebellar-pontine angle, are indistinguishable, these cases serve to make us more vigilant for potential delayed radiation-induced transformation of benign schwannomas. We advocate that the exponential clinical experience in focused radiation in nervous system tumors, should be matched by increased molecular understanding of its radiobiological consequences.

# SURGERY

**SURG-1**

**Parameningeal alveolar rhabdomyosarcoma of anterior skull base in adult: Case report and review of the literature**

*AK Bhattacharyya*, M Al-Gahtany, F Gentili (Toronto, Ontario)*

Parameningeal alveolar rhabdomyosarcoma of the anterior skull base is a rare neoplasm in the adult population. Only a handful of cases have been reported to date and in every case the diagnosis has been revealed as a histopathological surprise. We report the only case of this unusual entity treated in our institute in last 15 years.

A 23-year-old female presented with generalized headache and bilateral extraocular muscle paresis for 1 month and rapid deterioration of vision of both eyes for four days. MRI revealed the presence of a heterogeneously enhancing invasive anterior skull base tumor with sellar, supra-sellar, para-sellar and sphenoid sinus extensions. To decompress the optic apparatus an emergency trans-sphenoidal surgery and partial removal of the tumor was done.



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Postoperatively she had partial recovery of vision of the right eye. Subsequently she was treated with radiation and chemotherapy.

The clinical presentations, the treatment and the prognosis of parameningeal alveolar rhabdomyosarcoma of the anterior skull base are discussed.

**SURG-2**

**Transbasal meningiomas – A distinct clinical entity?**

*AK Bhattacharyya*, S Santoreneos, F Gentili, M Al-Gahtany, P Gullane, J Irish, W Halliday (Toronto, Ontario)*

A retrospective analysis of histologically benign cranial base meningiomas operated during the past 18 years (1985-2003) revealed an interesting cohort of tumors with complex extension into both the intra- and extra-cranial compartments (transbasal). Nineteen such cases were identified, 6 of which presented as "transbasal" meningiomas *de novo* and the remaining 13 as recurrent tumors following previous resections of intracranial skull base meningiomas without extracranial extensions. The extracranial extensions into nasopharynx, paranasal sinuses, orbits, infratemporal and pterygopalatine fossae resulted in a variety of symptoms including proptosis, soft tissue swelling, facial pain, nasal obstruction and discharge. Acombination of extended subfrontal, transbasal, fronto-orbito-zygomatic, mid-face/lateral rhinotomy and subtemporal-preauricular infratemporal fossa approaches were used and tailored according to the locations and the extents of the tumors. Total resection was achieved in only 3, near total in 12 and subtotal in 4 cases. The benign nature of the histology was confirmed by MIB-1 labelling index as well as immunohistochemistry (SPARC). After initial resection, recurrence was observed in 7 cases (36.8%) during a follow-up period between 4 months and 18 years. Quality of life (QOL) was assessed by age specific analysis of SF-36 scores and it was found to be comparable to that of the normal population until the age group of 65-74 years after which it decompensated significantly.

Cases of cranial base meningiomas with complex transbasal extensions have been mentioned as isolated cases in large series. Very few attempts have been made to study the complex behavior, propensity of recurrence and functional outcome of this interesting entity with deceptively benign histology.

**SURG-3**

**Correlation between neuroimaging and final pathology in patients undergoing stereotactic brain biopsy**

*C DeSilva*, A Kirkwood, D Lee, R Hammond, J Megyesi (London, Ontario)*

*Background:* The goal of this study was to determine how well the neuroimaging diagnosis correlates with the final pathological diagnosis on tissue obtained from stereotactic biopsies in patients with intracranial lesions.

*Methods:* The charts of 81 patients who underwent stereotactic brain biopsy at the London Health Sciences Centre between 1998 and 2002 were reviewed. The neuroimaging reports (MRI and/or CT) and the final pathology reports were independently analyzed and compared by two of the authors (neither being a neuro-radiologist or a neuropathologist). The final pathology report was deemed to represent the correct diagnosis.

*Results:* Neuroimaging provided a single clear diagnosis for 28/81 patients (35%), an uncertain diagnosis (one diagnosis preferred, but others suggested) for 16/81 patients (19%), and was indeterminate (multiple diagnoses suggested) for 37/81 patients (46%). Overall, neuroimaging correctly identified the tissue diagnosis in 26/81 patients (32%). Final pathology confirmed 68% of single neuroimaging diagnoses (19/28) but only 44% of uncertain diagnoses (7/16). Moreover, the accuracy of neuroimaging depended on the specific diagnosis: a neuroimaging diagnosis of high-grade glioma was correct 86% of the time, a neuroimaging diagnosis of low-grade glioma was correct 80% of the time , and a neuroimaging diagnosis of metastases was correct 29% of the time. A specific neuroimaging diagnosis of glioblastoma multiforme was correct 100% of the time.

*Conclusions:* In most situations a neuroimaging diagnosis should be confirmed by a tissue diagnosis.

**SURG-4**

**Stereotactic biopsy of intracranial lesions: Correlation between frozen section and final pathology**

*C DeSilva*, A Kirkwood, R Hammond, J Megyesi (London, Ontario)*

*Background:* The goal of this study was to determine the accuracy of frozen sections obtained at the time of stereotactic brain biopsy.

*Methods:* The charts of 91 patients who underwent stereotactic brain biopsy at the London Health Sciences Centre between 1998 and 2002 were reviewed. The frozen section and final pathology reports were independently analyzed and compared by two of the authors (neither being neuropathologists). The final pathology report was deemed to represent the correct diagnosis.

*Results:* Frozen section identified 84 patients as having tumorous lesions, of which 83 (99%) were confirmed. Frozen section identified 7 patients as having non-tumorous lesions, all of which were confirmed (100%). Of the tumorous lesions, frozen section identified 70 cases of glioma, of which 65 (93%) were confirmed, and 14 cases of non-glioma, all of which were confirmed (100%). The accuracy of frozen section for specific diagnostic categories was: inflammatory lesions (100%), meningioma (100%), high-grade glioma (88%), lymphoproliferative disorder (86%), metastases (83%) and low-grade glioma (58%).

*Conclusions:* Frozen section is excellent at differentiating a tumorous lesion from a non-tumorous lesion. This information may help initiate a patient's treatment planning. Frozen section is fairly good at differentiating glioma from non-glioma. However, a specific diagnosis, and definitive patient treatment, should await the final pathology report.

**SURG-5**

**Functional MRI in patients with brain tumor: Significance of shift in language areas**

*L Korngut*, S Mirsattari, Y-F Yen, A Takahashi, D Bandur, D Lee, J Megyesi (London, Ontario)*

*Background:* Tumors involving the language areas of the brain can alter language functions. Functional MRI (fMRI) reliably maps cortical activations during language tasks. We used fMRI to study the organization of anatomic locations of language areas in patients



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with brain tumors and correlated them with formal language testing.

*Methods:* Three right handed adult patients (average age: 53 years) with a primary brain tumor were studied. They all had language testing that included the Boston Naming Test and the Western Aphasia Battery.

*Results:* Anterior language areas were only minimally shifted forward and superiorly in one patient with a slowly growing and longstanding tumor involving the left anterior temporal lobe. This patient was mildly impaired in her formal language testing. The anterior language areas were markedly shifted forward to homologous regions of both frontal lobes in the second patient with a large malignant astrocytoma who was most severely impaired in formal language testing. There was no shifting of the language areas in the third patient with malignant astrocytoma whose language impairment was intermediate.

*Conclusions:* Reorganization of the language functions can occur in adult patients with brain tumor. Major anatomical shift in language areas seems to correlate with greater severity of aphasia on language testing.

**SURG-6**

**The histopathology of the cortical sealant Tisseel at reoperation**

*M Labib* (Montreal, Quebec); DA Ramsay (London, Ontario); J Richardson, M-C Guiot, RF Del Maestro (Montreal, Quebec)*

*Background:* The fibrin adhesive (Tisseel) has been used for closing cortical and ependymal defects following intraventricular and paraventricular tumour resection. The purpose of this study was to evaluate the physical and pathological changes that Tisseel undergoes at the site of application

*Methods:* Three patients who underwent a repeat operation in whom Tisseel was used to seal a cortical defect are included. The time period between the two operations is 2, 9, and 12 months. The morphology of the fibrin membrane and its physical stability were assessed during the second operation. Intraoperative specimens of the fibrin membrane were processed for histological examination.

*Results:* Athickened, opaque, watertight, arachnoid-like membrane covered the cortical defects. This membrane was not attached to the dura. Histologically, the moderate inflammatory reaction observed at 2 months after surgery disappeared by the 8th month. The density of the proliferating blood vessels in the granulation tissue seen at 2 months decreased by the 9th month leaving a well-organized fibrovascular matrix by one year.

*Conclusion:* Fibrin adhesive is physically stable and biologically tolerable in a CSF-rich environment. This product can be used effectively in sealing cortical defects during neurosurgical procedures, and reoperations can be easily performed through the fibrin sealant.

**SURG-7**

**The role of radical resection in the treatment of glioblastoma multiforme: A critical review of the recent literature**

*E Marmor*, S Prescott, C Wolfson (Montreal, Quebec)*

*Object:* The role of extensive surgical resection in the treatment of patients with glioblastoma multiforme remains questionable as evidenced by the continued publication of case series investigating this problem. The objective of this study is to conduct a critical review of the recent literature to determine the level of evidence available to resolve this dilemma.

*Methods:* All English language publications on adult glioblastomas published between January 1990 and December 2003 were reviewed. Only papers where extent of resection was examined as a prognostic variable were selected. Publications in which glioblastomas were not clearly separated from other pathologies were excluded.

*Results:* Fifteen of 4582 publications met these criteria. Of these, only two contained data collected prospectively and none were randomized. Assessment of degree of tumour resection varied widely. Twelve of the papers, including two using prospectively collected data, found a statistically significant survival benefit associated with extent of tumour resection, although this benefit was often small.

*Conclusions:* The majority of recent investigations suggest that radical resection of glioblastomas confers a survival advantage. Although the level of evidence is not high, it is unlikely that any better studies will be feasible in the near future.

**SURG-8**

**Pituitary adenoma metastasis: Review and classification**

*AJ Sabbagh*, R Leblanc, M-C Guiot, K Asaadi, D Melançon (Montreal, Quebec)*

*Background:* Pituitary adenomas occasionally spread to distant intracranial, spinal or systemic sites. Adenomas that do so are considered by many to be pituitary carcinomas regardless of their histo-pathological features.

*Methods:* One hundred and seven cases, diagnosed with metastasis from pituitary adenoma, gleaned from the literature along with a case from our institute, were analyzed.

*Results:* The average latency from diagnosis to metastasis was 7.6 years. All sites of the neuraxis were involved. The liver was the most common site of systemic involvement but metastases to bone, lymph nodes, and lungs were also seen. Most adenomas secreted prolactin (PRL) and adenocorticotraophic hormone (ACTH) (37 and 33 cases respectively). Twenty-eight were hormonally inactive (HI). ACTH secreting and HI tumors favored systemic and intracranial metastasis respectively, whereas PRL secreting adenomas metastasized to both. Surgery and/or radiation therapy preceded metastasis in 92% of the cases. Only 3 cases in addition to ours seeded by direct implantation during pituitary surgery.

*Conclusion:* Metastasis or seeding from a pituitary adenoma can occur (1) through direct intraoperative implantation, (2) from seeding within the CSF or (3) through hematogeneous or lymphatic pathways. The first type is likely less malignant. One should be aware of the possibility of pituitary adenoma metastasis especially after treatment.

**SURG-9**

**Tumor size, molecular profile and resectability of oligodendrogliomas and oligo-astrocytomas**

*AJ Sabbagh*, C Santguida, M-C Guiot, J Richardson, A Olivier, M Maleki, A Sadikot, D Sirhan (Montreal, Quebec); R Pokrupa (Kingston, Ontario); RF Del Maestro (Montreal, Quebec)*

*Background:* Completeness of surgical resection of oligodendrogliomas and oligo-astrocytomas may improve patients survival.

*Methods:* Charts and images of patients diagnosed with



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oligodendrogliomas and oligo-astrocytomas tumors were retrospectively reviewed to asses the influence of age, sex, clinical presentation, tumor size, location, and 1p/19q loss of heterozygosity (LOH) on surgical resectability.

*Results:* Forty-nine patients were included with a median age of 35 years. Fifteen patients (30%) had near complete resection (CR) defined as > 90 % (stereotactic biopsies excluded), 34 (70%) patients had partial resection (PR). The median maximum diameter for all tumors was 5 cm (4 cm in totally resected and 7 cm in partially resected tumors). Of tumors < 5 cm in maximum diameter, 63% had CR. Only 2 tumors > 5 cm had CR (both had LOH). Tumors with LOH were < 5 cm in 75% of cases and 78% of those had CR. Tumors with no 1p/19q LOH were < 5 cm in 29% of cases and only 50% of these had CR. Nine (20%) tumors involved deep structures, only one had CR.

*Conclusion:* Size and location are crucial factors affecting surgical resectability of oligodendrogliomas and oligo-astrocytomas. Patients harboring tumors with 1p/19q LOH become symptomatic at an earlier size and were more surgically resectable when compared those with no 1p/19q LOH.

**SURG-10**

**Diagnosis and management of brainstem gliomas in adults**

*B Sade *, G Mohr, E Marmor, K Sultanem (Montreal, Quebec)*

*Background:* Brainstem gliomas are rare in adults. There is ongoing controversy regarding the role of biopsy. This study aims at reviewing the experience of a single institution in the management of these difficult lesions and identifying possible factors affecting outcome.

*Methods:* Fifteen adult patients with brainstem gliomas were reviewed retrospectively (1993-2003). Survival outcomes were evaluated according to age, gender, symptom duration, MRI findings and pathology: 9 females and 6 males with average age of 43; tumor location midbrain in 5 patients, pons in 5 and medulla in 5. Pathology was verified in 10 patients via open biopsy in 4 and debulking in 6 (low grade 5 and high grade 5). Five patients had cerebrospinal fluid diversion procedures. Eight patients underwent external beam radiation.

*Results:* Eleven patients are alive (mean follow-up 40 months) and 4 died. Histological grade was the most important factor affecting survival: 4 patients with high grade lesions died and one is deteriorating. Low grade lesions remained stable over prolonged periods. Short symptom duration, contrast enhancement and cystic degeneration on MRI were also suggestive of unfavorable outcome.

*Conclusions:* MRI findings show good correlation with histological patterns and appear useful in establishing diagnosis as well as predicting outcome. However, biopsy is warranted when MRI is inconclusive.

**SURG-11**

**Development of a clinical and molecular genetic database for oligodendroglial tumors**

*S Abid* (Hamilton, Ontario); S Kamel-Reid (Toronto, Ontario); H McCarter, R Lai, J Provias, M Sur, N Murty, W McMillan, A Whitton, D Saltman (Hamilton, Ontario)*

Previous studies have demonstrated the utility of using molecular genetic markers in the clinical management of patients with oligodendroglioma and mixed oligoastrocytoma tumors. In these tumors, the demonstration of loss of heterozygosity (LOH) for 1p and 19q is associated with chemotherapy sensitivity and a longer survival, whereas LOH for 10q (in oligodendroglial tumors) may be associated with a worse prognosis. A database has been established by the Juravinski Cancer Centre neuro-oncology group to correlate oligodendroglioma and mixed oligoastrocytoma clinical characteristics, molecular marker study results and treatment outcomes. For LOH studies, DNA was extracted from blood and representative brain tumor tissue and then amplified by PCR using primers specific for microsatellite markers located on chromosomes 1p, 19q, and in some cases, 10q. To date, a total of 45 patient have been entered into the database with completed molecular genetic studies. Clinical characteristics for these patients include: demographics, histology at diagnosis, treatments, extent of surgical resection, neuroradiology (including the presence of pre-operative enhancement), time to progression and, when available, overall survival. The information from our database will enable more tailored and individualized therapy for patients with oligodendroglial tumors at our institution and may lead to ideas for prospective research. A summary of our data will be presented.

**SURG-12**

**Intramedullary melanotic schwannoma**

*C Santaguida*, AJ Sabbagh, J Richardson, M-C Guiot (Montreal, Quebec); R Pokrupa (Kingston, Ontario); P Kavan, RF Del Maestro (Montreal, Quebec)*

*Background:* Intramedullary melanotic schwannomas are very rare with only 4 reported. We outline a case of an intramedullary melanotic schwannoma that has had a much more aggressive course than those presented in the literature.

*Case report:* A 35-year-old male presented with neck stiffness and paresthesia extending down his right arm upon neck extension. An MRI revealed an intramedullary lesion that extended from C4 to C5 levels. A gross total excision of the mass was carried out and the pathology was consistent with a melanotic schwannoma. Two years following resection the tumor recurred and the patient was treated with radiation therapy. The tumor progressed two years following radiotherapy and at repeat resection multiple pigmented foci were present on the surface of the spinal cord and dura consistent with metastatic seeding.

*Methods:* We reviewed the patient's records along with corresponding literature related to the theories for the etiology of intramedullary melanotic schwannomas.

*Conclusions:* We present a case of intramedullary melanotic schwannoma with unusually aggressive course and suggest that frequent postoperative imaging follow-up may be more important with this type of tumor. Our case is consistent with the hypothesis that undifferentiated primitive cells originating in the neural crest are trapped in the neural tube during neuralation and the latter give rise to these tumors.



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**SURG-13**

### Primary dural diffuse large B-cell lymphoma coexisting with reactive follicular hyperplasia

*LN Hazrati, W Mason, SK Reid, D Bailey, PT Shannon* (Toronto, Ontario)*

A 32-year-old woman presented with seizure and 3 month history of headache and intermittent blurred vision. Imaging showed multifocal, contrast-enhancing dural-based masses adjacent to both cerebral hemispheres, with additional involvement of the left cavernous sinus and periorbital region. Meningeal biopsy revealed florid follicular hyperplasia, with Bcl-2 negative lymphoid follicles containing well-organized networks of CD21 (+) dendritic cells. In addition, there were minority areas of CD20, CD79a (+) Bcl-2 negative diffuse large cell lymphoma. Molecular genetics demonstrated a monoclonal J-H rearrangement on the immunoglobulin heavy chain. She was treated with 5 cycles of CHOP and intrathecal methotrexate as well as whole brain irradiation, and is in clinical and radiological remission 4 years later. Primary dural B-cell lymphomas are exceedingly rare lesions, and the unique coexistence of this tumor with extensive florid follicular hyperplasia as well as the clinical course suggests that in this patient, the neoplasm may have been diagnosed in its early stages.

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