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15TH BIENNIAL CANADIAN NEURO-ONCOLOGY MEETING

FEBRUARY 9-11, 2012

ROSEWOOD HOTEL GEORGIA
801 WEST GEORGIA STREET
VANCOUVER • BRITISH COLUMBIA • CANADA

PROGRAM AND
ABSTRACTS

The Canadian Journal of Neurological Sciences does not assume any responsibility or liability for any errors in the abstracts.

PROGRAM

15th Biennial Canadian Neuro-Oncology Meeting
Vancouver, BC – February 9-11, 2012
Rosewood Hotel Georgia • 801 West Georgia Street • Vancouver, BC

Thursday, February 9

1200-1900	Registration/Group/Sponsor Meetings
1200-1600	Industry Sponsored Sessions/TBA
1600-1700	CBTC Annual General Meeting
1830-2200	Welcome Reception

Friday, February 10 – Basic Science Day

0700-0800	Breakfast
0815-0830	Welcome Address
0830-0930	Current Trends and Future Directions in Cancer Genomics *Marco Marra, PhD, FRSC* *Director, Michael Smith Genome Sciences Centre* *Canada Research Chair in Genome Science, UBC* *BC Cancer Agency, Vancouver, BC*
0930-1030	Scientific Session One/Basic Science (Abstracts S1 -4)
1030-1100	BREAK
1100-1200	Scientific Session Two/Basic Science (Abstracts S5 – 8)
1200-1300	LUNCH
1300-1400	Current Trends and Future Directions in Cancer Stem Cells Science *Charles Eberhart, MD, PhD* *Associate Professor of Pathology, Ophthalmology, and Oncology* *Director of Neuropathology, Chief of Ophthalmic Pathology,* *Johns Hopkins University School of Medicine, Baltimore, USA*
1400-1500	Scientific Session Three/Basic Science (Abstracts S9 -12)
1500-1530	BREAK
1530-1700	Breakout Session One
1700-1800	Scientific Poster Session (Abstracts SP1 – 15)
1800-2000	Wine Tasting & Tour at Vancouver Art Gallery
2000-2200	Dinner at Hotel Rosewood Georgia

Canadian Brain Tumour Consortium Young Investigator Award in Basic Science

Stephen Mack (Sickkids Hospital, Toronto, ON, Canada)

Delineation of two clinically and molecularly distinct subgroups of posterior fossa ependymoma

With thanks to MERCK Canada and the Canadian Brain Tumour Consortium for a generous donation of $2500 to make this award possible.

Saturday, February 11 – Clinical Science Day

0700-0800	Breakfast
0800-0900	Current Trends and Future Directions in Radiotherapy for Meningioma *Michael Brada, MD* *Professor of Clinical Oncology* *The Institute of Cancer Research and* *The Royal Marsden NHS Foundation Trust, Sutton, United Kingdom*
0900-1000	Current Trends and Future Directions in Glioma Surgery *Mitchel S Berger, MD, FACS, FAANS* *Professor and Chairman, Department of Neurological Surgery* *Kathleen M. Plant Distinguished Professor* *Director, Brain Tumor Surgery Program* *Director, Neurosurgical Research Centers, Brain Tumor Research Center, UCSF*
1000-1030	BREAK
1030-1200	Scientific Session Four/Clinical Science (Abstracts C1-6)
1200-1300	LUNCH
1300-1400	Current Trends and Future Directions in Glioma Clinical Trials *Timothy Cloughesy, MD* *Director, UCLA Neuro-Oncology Program* *Clinical Professor* *The Ronald Reagan UCLA Medical Center, Los Angeles, CA, USA*
1400-1500	Current Trends and Future Directions in Pediatric Medulloblastoma *Eric Bouffet, MD* *Neuro-Oncologist, Professor of Pediatrics, University of Toronto* *Director of Neuro-Oncology Section, Division of Hematology/Oncology* *Hospital for Sick Children, Toronto, Canada*
1500-1530	BREAK
1530-1700	Breakout Session Two
1700-1800	Clinical Poster Session (Abstracts CP1 – 22)
1830-2000	DINNER/Grouse Mountain

Canadian Brain Tumour Consortium Young Investigator Award in Clinical Investigation

Robert Kosztyla (BC Cancer Agency, Vancouver, BC, Canada)

A radiotherapy planning study of high-grade glioma contouring on magnetic resonance imaging (MRI) and ^{18}F-FDOPA positron emission tomography (PET) with multiple observers

With thanks to MERCK Canada and the Canadian Brain Tumour Consortium for a generous donation of $2500 to make this award possible.

ABSTRACTS

Scientific Oral Presentations
10th February 2012

S1 – Session1 – 0930-0945

Irinophore C (IrC), a liposomal formulation of irinotecan, in combination with temozolomide (TMZ) to treat an orthotopic glioblastoma model

M Verreault[1], D Strutt[1], D Masin[1], M Anantha[1], D Walker[2], F Chu[2], D Waterhouse[1], DT Yapp[1], MB Bally[1]*

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Improved treatment outcomes linked to IrC-induced vascular normalization and associated enhancements in TMZ delivery. Despite aggressive therapeutic interventions, the 5-year survival rate of glioblastoma (GBM) patients remains less than 10%. One of the reasons for treatment failure in GBM is the poorly perfused nature of the tumor vasculature, which impedes delivery of therapeutic molecules across the tumor tissue. Research focused on new therapeutics delivery approaches is thus needed to define strategies that will improve the efficacy of GBM treatment. Our laboratory reported previously that IrC induces vascular normalization in an orthotopic model of GBM. The aim of this study was to assess whether treatment with IrC could increase the delivery of TMZ through a mechanism that involves vascular normalization and, in turn, to assess whether the therapeutic efficacy of the combination of IrC and TMZ was improved compared to TMZ treatment alone. The effects of IrC treatment on the tumor vasculature, on the delivery of TMZ to the tumor tissue and on the therapeutic efficacy of TMZ were thus compared to those observed following treatment with the unencapsulated form of the drug, irinotecan (IRN). It is demonstrated that IrC treatment, but not IRN treatment, induces changes in GBM vascular structure and increases delivery of TMZ by 2.5-fold to GBM tumor tissue. The combination of IrC and TMZ resulted in the best treatment outcomes, with 50% long term survivors (>180 days) in comparison to 17% long term survivors in animals treated with IRN and TMZ or TMZ alone. These results highlight the therapeutic potential of IrC combined with TMZ to achieve improved treatment outcomes in GBM.

S2 – Session1 – 0945-1000

Identification of MRI Biomarkers and Histopathological Alterations in Response to Combinatorial Therapy with Anti-angiogenic Agents and Radiation in a Murine Model of Glioma Tumor

Shahrzad Jalali, Warren Foltz, Kelly Burrell, Caroline Chung, Gelareh Zadeh

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Combinatorial therapy using radiation therapy (RT) and anti-angiogenic agents (AA) holds great promise in treatment of gliomas, however the exact scheduling of therapy has not established yet. To optimize the scheduling of RT and AA, there is a growing need to develop non-invasive, reproducible and quantitative biomarkers of response to therapy. This study aims to identify multi-parametric MRI biomarkers that can effectively determine tumor vascular changes in response to AA and RT. We compared results between two AAs (Sunitinib or VEGF-TRAP) in combination with RT in pre-clinical glioma models. Mice with intracranial tumors treated with AA, RT or AA+RT, and no treatment for control. Serial multi-parametric MRI analysis was acquired at different time points and correlative histological analysis was performed. We demonstrate a significant reduction in Ktrans (an index of vascular permeability) in RT or RT+AA groups which was associated with a reduction in tumor vascular density and vascular diameter. ADC (reflective of tumor cellularity and extracellular water content) significantly increased in RT versus non-RT groups and paralleled by a diminished tumor cell proliferation and increased intercellular space. VEGF-TRAP had greater effect on tumor growth and vessel permeability compared to Sunitinib. Combinatorial treatment showed a prolonged effect on reducing tumor growth and vascular density than RT or AA alone. The results of this study identify novel biomarkers of response to combinatorial therapy that can be used efficiently to schedule the sequence of AA and RT. Future work will focus on validating these biomarkers in clinical trials for patients with gliomas.

S3 - Session1 – 1000-1015

Normal brain response to ionizing radiation: BMDC recruitment

K Burrell, S Jelveh, R Hill, G Zadeh*

University Health Network, Toronto, ON, Canada

Introduction: Though radiation therapy plays a pivotal role in treatment of a wide range of brain tumors, the molecular mechanisms of adverse radiation effects following cranial irradiation (CR) is poorly understood. We explored the role of Bone Marrow Derived Progenitor Cells (BMDC) in response to CR.

Methods: Using co-culture experiments with BMDC and astrocytes, glioma and endothelial cells we examined whether BMDC play a protective role against irradiation in a temporal

and dose dependent manner. For in-vivo studies we used chimeric mice created by reconstituting the bone marrow (BM) of NOD/SCID mice with BM harvested from GFP transgenic mice. Intracranial windows (ICW) were created and with a stereotactic micro-irradiator radiation delivered through the ICW to normal brain. Two-photon microscopy was used to obtain high-resolution real-time in-vivo images dynamically tracking GFP+ BMDCs intracranially.

Results and Conclusion: Our key novel findings are that a specific radiation and dose dependent recruitment of BMDCs occurs following CR. BMDC migrate outside the vessel lumen to encircle the vessel in part as smooth muscle cells, inflammatory cells and microglia, possibly providing a vascular support or reparative role. Our results demonstrate that inflammatory cells are BM derived rather than brain resident in response to CR. Most notably we provide evidence that recruited BMDC differentiate to form microglia and more than 50% of microglia post-CR are not resident microglia but derived from BM. Our results support a protective role for BMDC in response to CR, suggesting a therapeutic role for BMDC in preventing adverse radiation effects.

S4 - Session1 – 1015-1030

Connexin43 in stromal astrocytes enhances glioma invasion

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Department of Cellular and Physiological Sciences, Life Sciences Institute, The University of British Columbia, Vancouver, Canada

The lack of gap junction intercellular communication (GJIC), mediated by the gap junction family of proteins, is a well established characteristic of advanced human cancers. Connein43 (Cx43) is highly expressed in adult astrocytes and its level is reduced in brain tumors of glial origin. Astrocytomas are classified into 4 grades according to WHO, with grade IV corresponding to the most aggressive glioblastomas. The decrease in Cx43 protein levels in high-grade gliomas is consistent with gap junction proteins being growth suppressors. However, the role of Cx43 as a modulator of tumor microenvironment and therefore indirectly affecting tumor behavior has not been explored. Cx43 is upregulated in reactive astrocytes during gliosis that often accompanies brain injury or inflammation. Similarly, a band of reactive astrocytes showing upregulation of glial fibrillary acidic protein (GFAP) and Cx43 protein has been observed at the tumor-host cell interface when mouse GL261 glioma cells were implanted intracranially into the brain of syngeneic C57BL/6 mice with an intact immune system. To explore the possibility that Cx43 may be important in direct tumor-host cell interaction, we implanted GL261 cells into Cx43 deficient Cx43fl/fl:Nestin-Cre mice and observed a reduction of glioma invasiveness in vivo, as indicated by the decrease of uneven tumor border attributed to the presence of invasive cells breaking away from the tumor core. The reduction of Cx43 protein by shRNA knockdown in GL261 glioma cells also decreased the proportion of migrating glioma cells at the tumor boundary. Our results reveal a direct role of glial cells, via GJIC, in promoting glioma invasion into the brain parenchyma.

Supported by a grant from the Canadian Institutes of Health Research (WCS and CCN). CCN holds a Canada Research Chair.

S5 – Session2 – 1100-1115

Delineation of two clinically and molecularly distinct subgroups of posterior fossa ependymoma

S Mack[1], H Witt[2], S Pfister[2], MD Taylor[1]

[1]Sickkids Hospital, Toronto, ON, Canada; [2]University of Heidelberg, Germany

Despite the histological similarity of ependymomas from throughout the neuroaxis, the disease likely comprises multiple independent entities, each with a unique molecular basis. In an effort to dissect the genetic heterogeneity of ependymoma, we performed gene expression profiling on two discovery cohorts of 102 and 75 ependymomas using two different gene expression array platforms. In both datasets, our findings support the existence of two molecularly distinct subgroups of PF ependymoma (Group A and B) that, although histologically similar, differ in their demographic, transcriptional, clinical, and outcome characteristics. Group A patients are younger, have laterally located tumors with a balanced genome, and are much more likely to exhibit recurrence, metastasis at recurrence, and death compared with Group B patients. Examination of the molecular pathways distinguishing Group A and B reveal two diverse patterns of genetic alteration suggesting that single targeted therapies are unlikely to be effective in the two different subgroups. We identified and optimized immunohistochemical markers of Group A (LAMA2 positive) and B (NELL2 positive), and validated our findings from the two discovery cohorts, in a third non-overlapping set of 265 PF ependymomas. Given the disparate outcomes of Group A and B patients, this assay provides a clinically relevant tool for prospective prognostication and stratification of PF ependymoma patients in future clinical trials. Further, the distinct molecular characteristics of these two classes of PF ependymoma suggest that subgroup-specific targeted therapies against subgroup-specific deregulated pathways are needed in future treatments of these tumors.

S6 – Session2 – 1115-1130

YB-1 bridges neural stem cells and brain-tumour initiating cells via is roles in differentiation and cell growth

Abbas Fotovati[1], Samah Abu-Ali[1], Pei-Shan Wang[1], Loic Deleyrolle[2], Cathy Lee[1], Joanna Triscott[1], James Y. Chen[1], Sonia Franciosi[1], Yasuhiro Nakamura[3], Yasuo Sugita[4], Takeshi Uchiumi[3], Michihiko Kuwano[5], Blair R. Leavitt[1], Sheila K. Singh[6], Alexa Jury[7], Chris Jones[7], Hiroaki Wakimoto[8], Brent A. Reynolds[2], Catherine J. Pallen[1], Sandra E Dunn[1*]*

[1]University of British Columbia, Vancouver, Canada, [2]University of Florida, Gainsville, Fla, [3]St. Mary's Hospital, Kurume, Japan, [4]Kurume University, Kurume, Japan, [5]Kyushu University, Fukuoka, Japan, [6]McMaster University, Hamilton ON, [7]The Institute for Cancer Research, Royal Marsden Hospital, Surrey, England, [8]Massachusetts General Hospital, Boston Massachusetts

The Y-box-binding protein-1 (YB-1) is up-regulated in many human malignancies including glioblastoma (GBM). It is also essential for normal brain development, suggesting that YB-1 is part of a neural stem cell (NSC) network. Here we show that YB-1 was highly expressed in the subventricular zone (SVZ) of mouse fetal brain tissues but not in terminally differentiated primary astrocytes. Conversely, YB-1 knock-out mice had reduced Sox-2, nestin and musashi-1 expression in the SVZ. While primary murine neurospheres were rich in YB-1, its expression was lost during glial differentiation. Glial tumours often express NSC markers and tend to loose the cellular control that governs differentiation therefore we addressed whether YB-1 served a similar role in cancer cells. YB-1, Sox-2, mushashi-1, Bmi-1 and nestin are coordinately expressed in SF188 cells and 9/9 GBM patient-derived primary brain-tumour initiating cells (BTICs). Silencing YB-1 with siRNA attenuated the expression of these NSC markers, reduced neurosphere growth and triggered differentiation via coordinate loss of GSK3-δ. Further, differentiation of BTIC with 1% serum or bone morphogenetic protein-4 (BMP-4) suppressed YB-1 protein expression. Likewise, YB-1 expression was lost during differentiation of normal human NSCs. Consistent with these observations, YB-1 expression increased with tumour grade (n=49 cases). YB-1 was also co-expressed with Bmi-1 (Spearmans 0.80, $p>0.001$) and Sox-2 (Spearmans 0.66, $p>0.001$) based on the analysis of 282 cases of high-grade gliomas. These proteins were highly expressed in 10/15 (67%) of GBM patients that subsequently relapsed. In conclusion, YB-1 is co-expressed with NSC markers where it functions to suppress cell growth and inhibits differentiation.

S7 - Session2 – 1130-1145

Identification of a molecular signature that depicts the most invasive brain tumor propagating cell populations

Ludivine Morrison[1], Robyn McClelland[1], Hiroaki Wakimoto[2], Tamra Werbowetski-Ogilvie[1]*

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Glioblastoma multiforme (GBM) is the most common and aggressive human malignant primary brain tumor. Following surgery and treatment, GBMs typically recur as a consequence of massive tumor cell invasion into the brain. While major research efforts have shifted towards characterizing brain tumor stem/propagating cells (BTSC) within the tumor mass, surprisingly little is known about the relationship between an invasive cell and a BTSC. As highly invasive cells elude current therapies and surgical resection, it has yet to be determined whether invasive cells are a BTSC subpopulation or a mutually exclusive cell type.

Here, we compared two patient-derived GBM stem cell lines, GBM8 and GBM4 that are highly invasive and non-invasive respectively. The highly invasive GBM8 exhibits a significantly lower self-renewal capacity compared to non-invasive GBM4. GBM8 and GBM4 neurospheres were subjected to a small antibody screen consisting of cell surface markers associated with neural lineage specification. We have identified two markers that are differentially expressed between GBM8 and GBM4. Interestingly, CD133 levels are higher in the invasive GBM8 that exhibits decreased self-renewal capacity. Importantly, the same cell surface markers were differentially expressed when we screened invasive and non-invasive single-cell-derived clones from a human medulloblastoma cell line, suggesting that this molecular profile is not cell-type specific. We are currently sorting brain tumor cells based on combinatorial surface marker expression to validate our findings in vitro and in vivo. Our molecular signature will be applied to drug discovery platforms to identify compounds that selectively target and eradicate highly invasive brain tumor/BTSC populations.

S8 - Session2 – 1145-1200

BNIP3 acts as transcriptional repressor of Death Receptor 5 (DR5) expression and prevents TRAIL induced cell death in malignant gliomas

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Glioblastoma (GBM) is the most common malignant brain tumor and current treatment modalities, such as surgical resection, adjuvant radiotherapy and temozolomide chemotherapy, are ineffective. Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) is a novel cancer therapeutic agent for GBM because of its ability to induce apoptosis in

glioma cells. Unfortunately, the majority of glioma cells are resistant to TRAIL-induced apoptosis. The Bcl-2 Nineteen kilodalton Interacting Protein (BNIP3) is a pro-cell death BH3-only member of the Bcl-2 family that is one of the most highly expressed genes in hypoxic regions of GBM tumours. We previously found that BNIP3 is localized to the nucleus in GBM and suppresses cell death in glioma cells. Herein, we have discovered that when BNIP3 nuclear expression is knocked down in glioma cell lines and in normal mouse astrocytes, TRAIL and its receptor DR5 expression are increased. In addition, when nuclear BNIP3 expression is increased, the amount of TRAIL induced apoptosis is reduced. Using a streptavidin pull-down assay, we found that BNIP3 binds to the DR5 promoter and knockdown of BNIP3 increases luciferase reporter activity of the DR5 promoter. Furthermore, nuclear BNIP3 expression in GBM tumours correlates with decreased DR5 expression. Taken together, we have discovered a novel transcriptional repression function for BNIP3 conferring TRAIL resistance in glioma cells. These results may provide a partial mechanism for why hypoxic cells in GBM survive despite aggressive therapies.

S9 – Session3 – 1400-1415

Detection of O6- and N7-methylguanine adducts by LC/MS in cell lines and brain tumour tissues obtained from patients treated with temozolomide

E Seyed Sadr[1], D Catana[2], A Tessier[3], M Seyed Sadr[1], J Alshami[1], C Sabau[1], R Del Maestro[1]*

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The current standard of care for glioblastoma includes surgery, radiotherapy and chemotherapeutic agents such as temozolomide (TMZ), a DNA methylating compound. The cytotoxic effects of TMZ have been linked to guanine methylation at the N7 and O6 positions. These adducts are not currently used as markers of TMZ efficacy. Using liquid chromatography/mass spectrometry (LC/MS), we have established a sensitive analytical assay to directly detect both N7- and O6-methylguanine adducts from DNA following TMZ treatment. A limit of detection of 1 fmol was observed for O6-methylguanine, while N7-methylguanine was observed below 5 fmol. O6- and N7-methylguanine were successfully detected by LC/MS in tumour and normal brain tissue samples from patients treated with a neoadjuvant TMZ regimen for 14 days (75 mg/m2). Variations in levels of both methylated guanines were detected between patients as well as within different locations of the same tumour sample. In addition, various concomitant treatment were investigated in vitro to determine possible increased potency of TMZ. This technique provides a direct detection of the damage inflicted by TMZ. This could potentially indicate the efficacy of the drug, allowing for prompt analysis and response. It also holds potential for determining efficacy of treatment dose, schedule and possible concomitant drugs.

S10 - Session3 – 1415-1430

Alkylpurine-DNA-N-Glycosylase confers resistance to temozolomide and poor survival in GBM

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[1]The Arthur and Sonia Labatt's Brain Tumour Research Centre, The Hospital for Sick Children's Research Institute, Univ. of Toronto; [2]EORTC Data Center, Brussels, Belgium; [3]Paterson Institute for Cancer Research, University of Manchester, Manchester, UK; [4]Department of Neuro-Oncology, The University of Texas M.D. Anderson Cancer Center, Houston, Texas 77401, USA; [5]Division of Pathology, The Hospital for Sick Children, Univ. of Toronto; [6]Laboratory of Brain Tumor Biology and Genetics, Department of Clinical Neurosciences, Centre Hospitalier Universitaire Vaudois and University of Lausanne, Switzerland. [7]Division of Neurosurgery, Toronto Western Hospital, Univ. of Toronto, ON, Canada

Glioblastoma multiforme (GBM) is the most common and lethal of all gliomas, with an average survival of 12-16 months. Current standard of care for GBM patients includes surgery followed by concomitant radiation and Temozolomide (TMZ). MGMT (O6-methylguanine-DNA methyltransferase) repairs the cytotoxic TMZ lesions, O6-methylguanine, and methylation of the MGMT promoter in GBM correlates with increased therapeutic sensitivity to alkylating agent therapy. However, several aspects of TMZ sensitivity are not explained by MGMT promoter methylation alone. We hypothesized that the base excision repair enzyme alkylpurine–DNA–N-Glycosylase (APNG), which repairs another cytotoxic lesion, N3-methyladenine and N7-methylguanine, might play a role in TMZ sensitivity. siRNA silencing of APNG in established and primary TMZ resistant GBM cell lines endogenously expressing MGMT and APNG, attenuated repair of TMZ-induced DNA damage and enhanced apoptosis causing reduced colony formation. Re-expression of APNG in TMZ sensitive GBM cells lacking MGMT and APNG enhanced the repair of TMZ-induced DNA damage and conferred partial resistance to TMZ. Immunohistochemistry (IHC) of GBM sections correlated lower APNG expression with epigenetic silencing of the APNG promoter. GBM patients with methylated MGMT promoter, who responded poorly to TMZ therapy, had high levels of APNG expression by IHC (P=0.001-0.03). In the EORTC-NCIC clinical trial, in patients with an unmethylated MGMT promoter, lack of APNG expression was a significant predictor of increased overall survival. APNG expression was not a predictor of survival in patients receiving radiation only. These in vitro and clinical data demonstrate that in addition to the MGMT promoter status, APNG expression also contributes to increased TMZ resistance in GBM.

S11 - Session3 – 1430-1445

Effect of Temozolomide Cytotoxicity on Mixed Populations of Brain Tumour Cells Exhibiting Different MGMT Expression

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Glioblastoma multiform (GBM) is an aggressive malignancy of the central nervous system associated with poor prognosis. Adjuvant and concomitant use of temozolomide (TMZ) with radiotherapy is the current standard of care for treatment of GBM patients. Epigenetic silencing of the O6-methylguanine-DNA methyltransferase (MGMT) promoter is a prognostic marker associated with prolonged overall survival of GBM patients. GBM tumours are morphologically and genetically heterogeneous displaying histological features that vary in different areas of the tumour. This study evaluates the effect of in vitro TMZ treatment on a mixed population of brain tumour cells exhibiting different MGMT expression, and explores possible extracellular interactions that may induce resistance to TMZ. We used wild type and transfected GBM and medulloblastoma cell lines that exhibit different MGMT protein expressions and/or MGMT promoter methylation levels. We performed in vitro cell culture assays after TMZ treatment to study three components of TMZ induced injury: 1. Cell lines sensitivity/resistance to TMZ treatment when cultured separately as compared to when cultured together in the same microenvironment. Initial data demonstrate that cell lines sensitivity to TMZ in a mixed cell population scenario is proportional to the MGMT promoter methylation levels in the total population of cells. 2. Using pyrosequencing analysis to compare the MGMT promoter methylation levels of cell lines before and after TMZ treatment. 3. To evaluate the N7/O6-methylguanine adducts levels in cell line post TMZ treatment. The levels of O6-methylaguanine remaining may indicate the extent of DNA repair performed in MGMT expressing cells as compared to MGMT non-expressing cells. These data should aid in the understanding of brain tumour cell resistance to TMZ treatment based on the heterogeneity of the tumour cell populations present in individual tumours.

S12 - Session3 – 1445-1500

Differentiating tumor recurrence from radiation necrosis in glioblastoma by use of diffusion tensor imaging

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Glioblastoma is the most common and aggressive primary brain tumor. Several lesions have been observed in the MRI images following radiotherapy, many of which fail to progress and are thought to be associated with radiation necrosis. It is challenging to differentiate these lesions from tumor recurrence. New and advanced techniques are needed for this purpose. Diffusion Tensor Imaging (DTI) is an MRI technique that is sensitive to damage of white matter tracts. It could show infiltration patterns that may not be visible using conventional imaging. In this study we use DTI to compute metrics such as axial (AxD) and radial(RD) diffusivity in patients with glioblastoma. Our hypothesis is that changes in the above mentioned metrics in the hyperintense regions, surrounding the resected tumor may be able to differentiate tumor recurrence from radiation necrosis. Four patients with glioblastomas were scanned initially and had follow-up MRI after three months. All MR scans were performed on a 3T Siemens Trio with a 32 channel head coil. The patients had tumor recurrence in parts of the hyperintense regions. Tumor recurred areas were identified on the post-gad T1-weighted images. The diffusion data was analyzed and, the axial and radial diffusivity values were computed from the volumes of interest. Reduced AxD and RD values were observed in the tumor recurred areas compared to the non-tumor areas in the edema. These lower values in the tumor may suggest disruption of the microstructurality resulting from the effects of tumor infiltration which represents increased isotropy.

Scientific Poster Presentations
10th February 2012

SP1

Tetrameric Right Handed Coiled Coil (RHCC) protein nanotubes as a modular delivery system for chemotherapeutics for effective killing of glioblastoma cells

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Departments of [1]Human Anatomy and Cell Science, [2]Surgery, [3]Medical Microbiology & Infectious Diseases, [4]Obstetrics, Gynaecology & Reproductive Sciences, [5]Chemistry, [6]Pathology, University of Manitoba, Winnipeg, MB, Canada

The archaebacterium Staphylothermus marinus produces tetrameric right handed coiled coil (RHCC) 24 kDa protein nanotubes that remain stable even at extreme temperatures, salt and pH conditions. We determined the crystal structure of RHCC and demonstrated a structural motif with four large cavities (320 – 360 Å3) inside a tetrameric channel capable of storing compounds. The cavities were loaded with the chemotherapeutic drug Cis-platin prior to crystallization at 3.2 Å resolution of the RHCC/cis complex in space group P3121 with unit cell dimensions of a, b=112.8 Å, c=71.6 Å and α, β=90˚, γ=120˚. Alexafluor488nm-labelled RHCC molecules were taken up by human glioblastoma cell lines and primary glioblastoma (GB) cells derived from patients as early as 6h after exposure. When U87 cells and primary GB cells were exposed to cisplatin-laden RHCC, we observed a strong and progressive cytotoxic effect with more than 80% GB cells killed at 72h incubation period, whereas empty RHCC had no effect. This cytotoxic effect on GB cells involved the activation of caspase 3/7 and a p53-mediated apoptotic pathway. In addition to cisplatin, we explored the ability of novel RHCC cargo compounds to kill GB cells. Gold chloride (AuCl4) also fits into the RHCC cavities and surpassed cisplatin in its ability to destroy GB cells. Our nanotubes can be targeted to specific structures/receptors exposed at the tumour cell surface and linked to antisense constructs to provide a novel combined strategy for efficient drug delivery of chemotherapeutic agents and signaling pathway interference in the treatment of brain tumour patients.

SP2

Targeting polo-like kinase 1 (PLK1) in brain cancer

Cathy Lee, Abbas Fotovati, Joanna Triscott, Sandra E. Dunn

CFRI, BC Children's Hospital, Vancouver, BC, Canada

In a genome-wide siRNA library screen of 691 kinases, we previously reported that polo-like kinase 1 (PLK1) inhibition suppressed the growth of pediatric sarcomas in vitro. In this study, we examined PLK small molecule inhibitor BI2536 for the treatment of primary brain cancers and specifically addressed the impact on brain tumour initiating cells (BTICs), given that they are often resistant to current therapies and as such are believed to facilitate relapse. PLK inhibition with siRNA or BI2536 significantly blocked growth, caused G2/M arrest and induced apoptosis of glioblastoma (GBM) and medulloblastoma cell lines. It also inhibited tumoursphere formation and Sox-2 expression. However, PLK1 inhibition did not affect the growth of immortalized human astrocytes. Of note, BI2536 suppressed the growth and/or self-renewal of SF188, and primary brain tumour cultures BT74 and BT241 that are temozolomide (TMZ)-resistant. Analyses of adult GBM (n=7), pediatric GBM (n=1), pediatric medulloblastoma (n=4) and pediatric supratentorial PNET (n=1) revealed that the patient-derived primary tumourspheres expressed ~110-470 times more PLK1 mRNA.

SP3

Role of YB-1 on glial tumours and its promise as a molecular target

J Triscott, SE Dunn

CFRI, BC Children's Hospital, Vancouver, BC, Canada

Glioblastoma multiforme (GBM) is an extremely aggressive brain tumor usually with poor prognosis. Currently, treatment with the only approved drug for GBM, Temozolomide (TMZ), often results in relapse as there is a high frequency of recurrence. Our laboratory has shown the oncogenic transcription factor Y-box binding protein-1 (YB-1) is overexpressed in GBM cancer cells compared to normal cells. The objective of this project is to understand how YB-1 facilitates drug resistance to TMZ and how the mechanism it uses to do this can be targeted for therapy. We show that TMZ treatment does not have an effect on cell populations that express high levels of YB-1, and survival of these cells may reestablish the tumour following treatment. To characterize the effect of silencing YB-1, we have treated cells with YB-1 siRNA, in the presence of TMZ, and used Affymetrix cDNA microarray technology to analyze changes in whole genome expression levels. Analysis shows ALDH5a1 is down regulated significantly and we are able to show enzyme activity is also affected when YB-1 is silenced in SF188 cells. ALDH5a1 may have a role in promoting tumour growth and survival. Therefore we hypothesize that inhibiting YB-1 or some of its downstream targets could be an alternative pathway to overcome TMZ resistance.

SP4

Concurrent CIC mutations, IDH mutations and 1p/19q loss distinguish oligodendrogliomas from other cancers

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Oligodendroglioma is characterized by unique clinical, pathological, and genetic features. We report the results of our concurrent effort to identify somatic mutations potentially contributing to 1p/19q co-deleted oligodendroglioma through a combination of exome, transcriptome, and whole genome shotgun sequencing on brain tumour initiating cell (BTICs).

All cases had mutations in either IDH1 or IDH2. In addition, we discovered somatic mutations and insertions/deletions in the CIC gene on chromosome 19q13.2. The overall mutation rate in CIC gene in oligodendrogliomas in this study was 69% compared to 2% in astrocytomas and oligoastrocytomas without 1p/19q.

Although we observed no differences in the clinical outcomes of CIC-mutant versus wild-type tumors, we hypothesize that the mutant CIC on the single retained 19q allele is linked to the pathogenesis of oligodendrogliomas with IDH mutation. Our detailed study of genetic aberrations in oligodendroglioma suggests a functional interaction between CIC mutation, IDH1/2 mutation and 1p/19q co-deletion.

SP5

Telomerase inhibition induces growth arrest in paediatric ependymoma

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Ependymomas represent the third most common paediatric brain tumour, yet effective chemotherapeutics are lacking and 5-year survival rates remain poor at approximately 50%. Previous studies have shown that the majority of ependymomas possess telomerase, an enzyme that maintains telomere length and permits limitless growth potential. The objective of this study was to elucidate whether telomerase is an effective therapeutic target in ependymoma using the telomerase inhibitors MST-312 and imetelstat. R254 and BXD-1425EPN paediatric ependymoma cells were first characterized for radial glial cell marker-2 (RC2), nestin, glial fibrillary acidic protein (GFAP) and telomerase activity. R254, BXD-1425EPN and telomerase-negative fetal neural stem cells (fNSCs) were then treated for 72 hours with MST-312. R254 cells were also treated with a second telomerase inhibitor (imetelstat) for 10 weeks in parallel with mismatch and untreated controls. Cell growth (MTT/count), apoptosis (tunel), senescence (beta-galactosidase), cell cycle arrest (flow cytometry) and DNA damage (gammaH2AX) were assessed. Both R254 and BXD-1425EPN cells possessed functional telomerase and stained positive for RC2, nestin and GFAP. MST-312 telomerase inhibition resulted in decreased cell growth, increased ✍H2AX associated DNA damage and increased G2 cell populations in ependymoma cells but not in telomerase-deficient fNSCs. Following five weeks of imetelstat treatment, R254 ependymoma cells displayed reduced growth rate associated with increased DNA damage and senescence. These findings suggest that telomerase inhibition may represent a potential therapeutic strategy for paediatric ependymoma.

SP6

SLIT2 inhibits brain tumour invasion by downregulating MMP14

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Introduction: Chemotropic cues such as Slit guide the migration of neural cell precursors during development. Slit and Roundabout (Robo) have been implicated in angiogenesis and leukocyte migration. Recent studies placing brain tumours in the context of neurodevelopment have led to the recognition of new genes involved in tumour progression. We have shown that SLIT2-ROBO1 signalling inhibits medulloblastoma (MB) cell invasion (Werbowetskie-Ogilvie et al. Oncogene 2006). We are expanding our observations by characterizing the SLIT-ROBO signalling pathways.

Methods: We have tested the transcriptional response of MB and glioma lines to exogenous SLIT by microarray analysis. We have validated the top transcriptional targets of SLIT proteins and we have assessed the biochemical interaction of MMP14 with ROBO1.

Results: Over 200 transcripts are altered in MB cells when treated by SLIT2. Our results indicate that MMP14 acts as a ROBO1 protease, capable of cleaving and inactivating it. ROBO1 cleavage leads to its rapid degradation. Furthermore, the cleaved ROBO1 ectodomain is still capable of binding SLIT proteins and preventing them from binding functional ROBO receptors. Finally, we have shown that knocking down MMP14 in brain tumour cells decreases cellular invasion.

Conclusions: This study demonstrates that MB cells respond specifically to SLIT by modulating transcripts necessary for cell invasion. Downregulating MMP14 expression in MB cells decreases invasion. Our results infer the possibility that altering known neuro-developmental pathways may be useful in modifying the invasive paradigm of brain tumour cells.

SP7

Expression of pannexin 2 in brain tumours

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Tumour cells often exhibit abnormal homocellular (tumour cell-to-tumour cell) or heterocellular (tumour cell-to-surrounding stromal cell) communication. This abnormal cell-to-cell communication suggests that gap junctions might play a role in the development of tumours. Although the role of gap junctions in cancer has predominantly been attributed to connexins, recent evidence indicates that pannexins (Panxs) might also play a pivotal role. Of the 3 Panx isoforms, only Panx1 and Panx2 are found in the brain. Although Panx1 and Panx2 are mostly detected in neurons, there is evidence that they are also expressed in various glial cells, including astrocytes, which play a role in brain tumour formation. In this regard, our group has previously shown that the re-introduction of Panx1 or Panx2 in C6 rat glioma cells reduce their oncogenicity. To further explore the significance of our previous findings, we used publicly available gene expression databases including the REpository for Molecular BRAin Neoplasia DaTa (REMBRANDT) and the Gene Expression Omnibus from NCBI (GEO) to determine the expression profile of Panxs in various brain tumour subtypes. Interestingly, there is an apparent down-regulation of Panx2 but not Panx1 mRNA expression in distinct subtypes of brain tumours such as oligodendroglioma and glioblastoma. To determine whether Panx2 protein follows the expression profile of its mRNA, we will characterize the expression of Panx2 protein in human glioma cell lines and primary brain tumour tissue arrays. Our preliminary results show that Panx2 protein is down-regulated in brain tumours compared to normal tissue. Moreover, we confirmed that Panx2 distribution is predominantly intracellular and therefore does not support a role for Panx2 in direct intercellular communication. Future work includes the determination of the subcellular localization of Panx2 in normal and tumour cells which might reveal a novel role of Panx2 in the formation of brain tumours.

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SP8

Targeting protein mutations driving high-grade brain tumors

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Routine laboratory diagnosis of high-grade glioblastoma (GBM) tumors currently consists of identification by light microscopy with clinical classification involving placement into either primary or secondary tumors on the basis of pathological features. Using next-generation sequencing technologies, a substantial effort has led to the identification of genetic mutations in GBM that might be used to help define patients with differing prognoses and/or therapeutic response. Although genetic mutations are best identified by DNA/RNA screens, we currently have little or no information how these aberrant genes translate into proteins. Collectively, the experiments described within this presentation will expand our current understanding of high-grade brain tumors by quantifying GBM mutations in a targeted and sensitive way using mass spectrometry. Our global hypothesis is that "protein mutation dose" (copy#/cell), will provide additional measures to help classify patient subpopulations. To this end, we are developing MS methods that will permit us to identify and quantify GBM mutations within a panel of human gliomas. To generate internal standards and expedite assay development, we have constructed a Mutant Peptide Database (MuPpt) using information housed within the Catalogue Of Somatic Mutations In Cancer (http://www.sanger.ac.uk/genetics/CGP/cosmic/). The analytical strategies described may have direct implications to other cancers and expedite the use of protein biomarkers in a clinical setting.

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SP9

Aurora kinase B inhibition in diffuse intrinsic pontine glioma has therapeutic potential

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Diffuse intrinsic pontine glioma (DIPG) represent the most devastating paediatric malignancy, for which current therapies are not effective and past clinical trials have been based on adult protocols. The development of future effective therapeutic modalities for this disease hinges on a better understanding of its biological properties. Here, eleven paediatric glioblastoma and nine DIPG samples were subject to gene expression profiling using the HumanWG-6 and HumanRef-8 beadchip arrays from Illumina. Array data was validated using quantitative real-time PCR and immunohistochemistry as well as cross-validation of our dataset with previously published series. We then went on to test AURKB inhibition using two aurora kinase inhibitors; reversine and VX-680 in two paediatric glioma cell lines and one mouse brainstem glioma cell line. AURKB was consistently and highly over-expressed in 6/9 DIPGs and 8/11 glioblastomas. Inhibition of AURKB activity in two paediatric glioblastoma cell line, SJ-G2 and SF-188 and one mouse brainstem glioma cell line by reversine and VX-680 resulted in growth arrest, accompanied by morphological changes, cell cycle aberrations, nuclear fractionation and polyploidy followed by cell death upon removal of the blockade in paediatric high grade astrocytoma cell lines. Soft agar colony formation assay resulted in reversine treated cells forming fewer and smaller colonies as compared to

vehicle treated controls. Our data highlights AURKB as a potential therapeutic target in paediatric glioblastoma including DIPG. Aurora kinase inhibitors are currently being investigated in clinical trials for several cancers and thus may be readily translated into a therapy for these patients.

SP10

Aurora Kinase A as a rational target for treatment of Malignant Peripheral Nerve Sheath Tumours

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Rationally-designed therapies and predictive biomarkers are required for rare tumours, such as the aggressive, NF1 mutation associated, malignant peripheral nerve sheath tumours (MPNST). Published analysis of copy number variation identified hemizygous loss of RHAMM in over half of the high-grade MPNST, but not in benign neurofibromas or low grade tumours. We have described RHAMM as a molecular brake for aurora kinase A (AURKA). Now, we propose that its loss in high grade MPNST may oncogene-addict tumours to this kinase and sensitize them to aurora kinase inhibitors (AKI). We have profiled two MPNST progression series for the expression and activity of AURKA as well as their responses to three AKI. We focused on the most proliferative lines, S462 and 2884, which express equivalent amounts of kinase. These lines differ in the expression of kinase regulators, like TPX2 (the accelerator) and RHAMM (the brake). Relative to 2884, S462 cells express significantly more TPX2 and significantly less RHAMM, which was quantified at the protein, message, and genomic levels. S462 also display elevated aurora A activity, as measured by the abundance of two downstream substrates, Histone H3-pS10 and RHAMM-pT703. All three AKIs reduced kinase activity in a dose-dependent manner. Cellular responses to AKI correlated to the activity, and not only the abundance, of AURKA. We find AKI are encouraging drugs for aggressive MPNST. Kinase substrates, like RHAMM-pT703, may serve as valuable biomarkers for tumour responses. Our future directions will further study molecular control of AKI sensitivity and test AKI in situ.

SP11

Identifying RNA and Protein Expression Profile of Bone Invading and Non-Invading Meningiomas

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Meningiomas are benign primary brain tumors however a subset causes hyperostosis and invasion of adjacent neural and soft tissues. Bone-invading meningiomas represent a significant clinical challenge since complete surgical resection is often impossible resulting in higher recurrence rates and repeat surgery. This study aims to identify differential gene and protein expression profile of bone-invading and non-invading meningiomas. Archived specimens of 75 patients were selected. RNA and Tissue Microarray were performed on the samples. Array data was verified using real-time PCR. Meningioma cell lines were used for in-vitro and in-vivo functional studies. Matrigel invasion assay, immunostaining and western blotting used to characterize the behavior of these cells in vitro. Intracranial meningioma tumors were generated and small animal MRI was used to study tumor growth pattern and behavior. RNA microarray data identified 222 differentially expressed genes of which the overexpression of MMP16 and 19 were selected as novel matrix remodeling metalloproteinases involved in bone invasion. In-vitro studies identified a direct correlation between invasive capacity of meningioma cell lines and expression level of MMP16 and MMP19. siRNA inhibition of MMP16 demonstrated diminished proliferation and invasion in-vitro and in-vivo. The downstream signaling pathways regulated by MMP16 were identified as MAPK and AKT. In vivo studies using xenograft meningioma tumor models showed the tumor growth and invasion to the underlying bone tissue and confirmed in vitro data. These results provide the basis of future studies to explore potential novel therapeutic strategies that can help control growth of bone-invasive meningiomas.

SP12

NFAT and T cell response play major roles in the formation of sporadic schwannomas

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Introduction: Even though clinical and morphological differences of vestibular schwannomas are well documented, the knowledge on molecular mechanisms of development is limited. In this study, we examined differences in gene expression between tumor and control tissue in search of underlying disease-causing deregulated pathways.

Material and Methods: We performed whole genome microarray expression profiling (HG-U219 Array Plate, Affymetrix) and pathway analysis of tissue samples from 36 patients with sporadic vestibular schwannomas versus seven postmortem samples of the vestibulocochlear nerve.

Results: 2.694 genes that were deregulated over 2fold were identified: 1.471 were up- and 1.223 downregulated. The most significantly deregulated pathways in vestibular schwannomas include the role of nuclear factor of activated t-cells (NFAT) in immune response, phospholipase C signaling and antigen presentation.

Conclusion: An important role in vestibular schwannoma formation is attributed to nuclear factors of activated T cells and their transcriptional partners whose combined interactions result

in a deranged T-cell response and may thereby lead to an imbalance between tumorigenesis and immune response.

SP13

p53 regulates inhibition of neurogenesis after cranial irradiation

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Background and Purpose: Neurocognitive dysfunction is a serious late effect of cranial irradiation (IR). Neurogenesis, a process associated with learning and memory function, is known to be inhibited after IR. Alterations in the p53 tumor suppressor gene are associated with tumor radioresistance. Whether p53 plays a role in the inhibition of neurogenesis after IR is unclear.

Materials and Methods: We irradiated adult male p53 +/+, +/- and -/- mice to determine the influence of p53 on neurogenesis and the different neural progenitor cell (NPC) populations in the dentate gyrus of the hippocampus after IR.

Results: As previously reported, p53 deficiency was associated with a significant increase in neurogenesis in the dentate gyrus of non-irradiated mice. In contrast, p53 deficiency had an independent profound inhibitory effect on the number of newborn neurons after IR (IR dose, $p<0.0001$; p53 genotype, $p = 0.0005$; dose and p53 interaction, $p<0.0001$, linear regression). NPCs were uniformly reduced after IR regardless of p53 genotype. However, p53 deficiency was associated with a marked reduction in the number of newly born type 1 NPCs, or the putative neural stem cells after IR (p53 genotype, $p = 0.0005$).

Conclusions: Inhibition of neurogenesis after IR is regulated by p53. These findings identify specific targeting of the p53 pathway as a novel approach to improve the therapeutic ratio of cranial RT.

SP14

Function of bone marrow derived cells recruited to tumor vasculature during progression

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Introduction: The role of bone marrow derived cells (BMDC) in tumor neo-vascularization remains controversial. We focused on the spatiotemporal contribution of BMDC to neo-vascularization in malignant brain tumors and in response to ionizing radiation (IR) and alterations in endothelial cell (EC) biology.

Methods: Intracranial glioma xenografts were created in chimeric mice with reconstituted GFP-fluorescent bone marrow with an intracranial window to allow examining in-vivo real time longitudinal pattern of recruitment, migration and differentiation of BMDC in response to tumor growth and IR. ECs were isolated from centre and periphery of the tumor using Laser Capture Microscope (LCM) and their differential genetic profile established with real-time PCR.

Results and Conclusion: At early stages of tumor formation there is 90% integration of BMDC uniformly throughout all tumor vessels while at later stages of tumor growth, 10% integration of BMDC is seen in the central vasculature compared with an almost 100% integration of BMDC in the peripheral vessels. BMDC differentiate to form pericytes, macrophages and microglia and not EC in the centre of the tumor. This novel finding of region dependent contribution of BMDC to tumor vascularization has significant therapeutic implications. Following IR BMDC incorporation in tumor vasculature is the same in the centre versus periphery and most notably based on the differential expression profile of EC, vessels in centre take on host derived characteristics rather than tumor cell characteristics. These results suggest that IR disrupts the capacity of tumor cells to promote angiogenesis and IR promotes a vasculogenic survival of cancer cells supporting tumor recurrence.

SP15

Metabolic modulation of GBMs by depleting hexokinase II: potentiating the effect of standard therapies

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A key biological difference between tumor cells and normal cells is their metabolism. Tumor cells undergo a metabolic switch whereby glucose metabolism shifts from oxidative-phosphorylation to aerobic glycolysis. Reliance of proliferating cancer cells on aerobic glycolysis, even in the presence of oxygen is termed the "Warburg Effect". We recently demonstrated that hexokinase2 (HK2) is a critical mediator of aerobic glycolysis in Glioblastoma Multiforme (GBM). Inhibiting HK2 resulted in decreased proliferation, and increased sensitivity to apoptotic inducers such as RT and temozolomide (TMZ). These in-vitro anti-tumorigenic effects of depleting HK2 were also reflected in intracranial GBM xenografts, where tumors showed reduced growth and survival. We hypothesize that inhibiting aerobic glycolysis by depleting HK2 will modulate resistance to apoptosis and sensitize GBMs to RT and TMZ in-vivo. We generated GBM cell lines with an inducible short-hairpin RNA system to direct conditional expression of HK2. Conditional HK2-loss results in decreased proliferation and reverts GBMs to normal oxidative metabolism whereby O2 consumption increases and lactate production decreases. The impact of conditional HK2-depletion on in-vivo growth will be evaluated by injection of tetracycline-regulated cells in orthotopic mouse xenografts. Bioluminescent imaging is used to establish the growth kinetics of GBM cell lines intracranially. The synergistic effect of loss of HK2 along with RT and/or TMZ will be evaluated to determine whether HK2 status influences the chemo and radio-sensitivity of GBMs. We postulate that reversing aerobic glycolysis by HK2-inhibition can improve the survival of glioma-bearing mice by sensitizing GBMs to cell death induced by RT and/or TMZ.

Clinical Oral Presentations
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C1

Treatment Outcome for 757 Patients with Glioblastoma in 3 Population-based Neuro-Oncology Centres

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Patients with Glioblastoma Multiforme (GBM) have historically had a median survival of 9-11 months after surgery and radiation therapy (RT). The addition of temozolomide (TMZ) to standard of care was supported by the 2005 Stupp study, which reported a median survival of 14.6 months. However, variation exists between and within patient populations. We examined three geographically distinct Canadian patient populations and evaluated the role of various prognostic factors.

Methods: Patients with GBM were identified at three Canadian centres, in two Canadian provinces, from prospectively collected databases of population-based neuro-oncology centres (years 2001-2008). Biopsy or extensive surgical debulking of the tumor was undertaken followed by RT, or RT with concomitant TMZ followed by 6-12 cycles of TMZ. MGMT promoter methylation status was assessed when possible.

Results: A total of 757 patients were analyzed from three centres: Calgary (n=352), Edmonton (n=211), and Halifax (n=194). The mean age was 60 years, 64% were male, and the overall median survival was nine months with no difference among sites (p=0.90). The median survivals for methylated (n=172) versus otherwise (n=585) was 12 versus 8 months, for debulking (n=485) versus biopsy (n=272) was 11 versus 5 months, and for RT+TMZ (n=423) versus otherwise (n=334) was 13 versus 4 months; p<0.001. A wider gradient of median survivals was achieved by assigning a value of 1 for each of methylated, debulking, and RT+TMZ and summing to a score between 0 and 3. The median survivals for patients scoring 0 (n=135), 1 (n=254), 2 (n=278), and 3 (n=90) were 3, 7, 12, and 19 months, respectively.

Conclusion: Interesting similarities and differences were noted among the three centres, yet patient outcomes (median survival) were very comparable. Patients undergoing surgical debulking of methylated tumors who had both radiation therapy and chemotherapy had the best outcome (median survival 19 months).

C2

A radiotherapy planning study of high-grade glioma contouring on magnetic resonance imaging (MRI) and ^{18}F-FDOPA positron emission tomography (PET) with multiple observers

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Introduction: Inter-observer variations in target volume contouring have important implications for radiotherapy delivery and outcome.

Methods: Nineteen patients with high-grade gliomas had computed tomography, gadolinium contrast-enhanced MRI and 3,4-dihydroxy-6-^{18}F-fluoro-L-phenylalanine PET imaging for radiotherapy planning. The imaging was fused in treatment planning software and five observers (one nuclear medicine physician and four radiation neuro-oncologists) contoured gross tumour volumes (GTVs) using "MRI" (CT and MRI) and "PET" (CT, MRI and PET). The MRI-GTV was defined as the gadolinium enhancement excluding the surgical cavity. The PET-GTV was defined as the union of the MRI-GTV and the ^{18}F-FDOPA tracer uptake excluding the surgical cavity. Clinical target volumes (CTVs) were defined as 2 cm margins on GTVs. The simultaneous truth and performance level estimation (STAPLE) algorithm was used to define consensus contours. The consensus contours were analysed using percent volume overlap (PVO = common volume / encompassing volume).

Results: By PVO, PET contours (45.1% +/- 21.5%) exhibited greater inter-observer agreement than MRI contours (30.5% +/- 23.2%). By linear regression, PET-GTV consensus volumes were 1.6 +/- 0.3 times larger than MRI-GTV consensus volumes ($p < 0.001$). The consensus PET-GTV extended beyond the consensus MRI-CTV in 58% of cases.

Conclusions: Inter-observer variation in high-grade glioma target contouring was better using PET than using MRI alone. Consensus PET-GTVs were significantly larger than consensus MRI-GTVs. The standard 2 cm margin from MRI-GTV to MRI-CTV definition led to geographic miss of the consensus PET-GTV in a majority of cases.

C3

High Dose Photon Radiotherapy for Skull Base Chordomas and Chondrosarcomas

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Skull base chordomas and chondrosarcomas are locally aggressive tumors at high risk of post-surgical recurrence. In the last ten years, image guided intensity modulated RT (IG-IMRT) has facilitated accurate delivery of photon RT with doses

comparable to proton RT. Twenty-seven patients with skull base chordomas or chondrosarcomas were treated using high-dose photon RT at our institution from August 2001 to May 2009. Fourteen patients had chondrosarcomas (Gr I:7, Gr II:6, Gr III:1) and 13 patients had chordomas. The median RT dose was 70 Gy (60 to 76 Gy) delivered in 2 Gy/fraction. All patients were treated with IMRT, 13 were immobilized using a relocatable stereotactic frame while the remaining 14 patients had thermoplastic masks. Cone-beam computed tomography was used for daily image-guidance in the last 18 patients. Five year local control and survival for chondrosarcomas were 93% and 85% respectively, and were 77% and 81% respectively for chordomas (median follow-up 53 months). In the chordoma group, one patient is alive with progressive disease, two patients died of locally recurrent tumour and one due to a radiation-induced malignancy. In the chondrosarcoma group, one patient died of locally recurrent disease and one from extra-cranial disease. In terms of long-term toxicity, two patients developed hypothyroidism, one hypopituitarism, and one RT-induced hearing loss. No patient had radionecrosis nor RT-induced vascular or cranial nerve injury. IG-IMRT photon radiotherapy has similar control rates and toxicity as seen in proton beam experiences.

C4

Bevacizumab (bev) for recurrent high-grade glioma (HGG): Canadian experience

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Bev + irinotecan improves overall response rate (ORR) and progression-free survival (PFS) in patients (pts) with recurrent HGG. We evaluated bev in consecutive pts with recurrent HGG in this retrospective chart review at McGill University, Canada.

Methods: Recurrent HGG pts (e18 years) receiving bev (5-10 mg/kg i.v. q2w) +/_ chemotherapy between Aug 2008 and Dec 2010 were included. Choice of treatment was at the physician's discretion. Primary and secondary endpoints were PFS, ORR, overall survival (OS), 6-month PFS, and safety. Response and time-to-event data were evaluated using MacDonald criteria and the Kaplan-Meier method, respectively.

Results: 27 pts with primary grade IV GBM (n=13) or secondary high grade glioma (glioblastoma) (n=14) were included. All had received prior chemotherapy either as first-line treatment or following subsequent relapse/recurrence. 22/27 pts received bev in combination with chemotherapy. Four pts received bev across multiple lines of treatment. Median PFS was 6.9 months (95% CI, 3.8_12.2); 6-month PFS rate was 59%. There was a clinically significant reduction in cerebral edema in 4 pts and steroid dose was decreased in 11 pts (41%). Eight pts developed bev-related grade 3/4 adverse events: venous thromboembolism (4.5%; single-agent bev); neutropenia (13.6%; bev + TMZ + procarbazine or lomustine); and thrombocytopenia (18.1%; bev + lomustine or TMZ). Updated efficacy and safety data will be provided at the time of presentation.

Conclusions: Our current results compare favorably with those from US and European studies and suggest that bev +/_ chemotherapy is tolerable and effective in pts with relapsed HGG.

C5

Supratentorial childhood ependymoma treated with surgical resection alone upfront: Canadian experience

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Introduction: Surgical resection alone is a consideration in children with supratentorial ependymoma (STE), data to support this however is limited.

Methods: We performed a retrospective review of children diagnosed with STE in 12 Canadian centres, between 1986 and 2006. The clinical data was acquired through standardised data forms, and chart review. Central review of pathology was performed. Kaplan Meier analysis of survival was performed. This report is limited to those patients treated with resection alone at time of diagnosis.

Results: Thirteen patients identified had a gross total resection (GTR >95% resection): 45% 5yr PFS; 68% 5yr OS. Five required no further therapy: median age 11.4 yrs (2.3-14.3). Median follow-up eight yrs (five to ten), all alive and independent. Three were salvaged at relapse: median age seven yrs (two to ten). Three salvaged with GTR and radiotherapy (2), plus chemotherapy (1). Median follow-up five yrs (four to six). Five died: four progression; one sepsis. 88% of survivors post GTR upfront had WHO grade 2 pathology.

Five additional patients were treated with incomplete resection followed by a period of observation: median age six yrs (1.8-10). Three were salvaged with surgery and radiation at progression, median follow-up eight yrs (2-13). One is progression free, follow-up ten mos. Relapse/progression was at the primary site in 92%.

Conclusion: Long-term survival is compatible with GTR alone in STE. Progression post surgery alone is salvageable with resection and XRT. More precise prospective evaluation of degree of resection and additional biomarkers may delineate which children can be treated successfully with this approach.

C6

A phase III randomized controlled trial of short-course radiotherapy with or without concomitant and adjuvant temozolomide in elderly patients with glioblastoma (NCIC CTG CE.6, EORTC 26062-22061, TROG 08.02)

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The EORTC (26981-22981)/NCIC CTG (CE.3) RCT in newly diagnosed GBM found improved survival with concomitant and adjuvant temozolomide (TMZ) added to radiotherapy (RT). Study pts were 18-71 (median 56) years, and a trend benefit analysis found less benefit with increasing age. A recent RCT in elderly GBM pts found improved survival with RT compared to supportive care alone and others detected non-inferiority of 40 Gy/15 vs a 60 Gy/30 RT regimen. Therefore, RT alone is considered standard for elderly pts. However, the question remains: does the addition of TMZ to RT confer a survival advantage in elderly pts for whom _short-course_ radiotherapy is recommended?

Study Design: In order to have 90% power to detect a 25% reduction in the primary outcome of overall survival (increased MST from six to eight months) between arms, using a two-sided 5% alpha, a minimum of 520 deaths must be observed prior to analysis, total sample size is 560 patients.

Study Progress: The trial is open in Canada (NCIC CTG), Europe (EORTC), Australia and New Zealand (TROG), and Japan and about to open through the ACTION network in the USA. As of Sept 30, 2011, 316 pts were randomized. Median age is 73 (65-88) years with 71% over the age of 70. 77% are ECOG 0 or 1 and 23% are ECOG 2; 71% had sub- or gross-total resection, 29% biopsy only. A planned futility analysis by the independent DSMB resulted in a recommendation that the trial continue.

Discussion: This RCT is an international cooperative effort addressing an important unmet need in the spectrum of care for newly diagnosed glioblastoma. Accrual is expected to be complete in 2013.

Clinical Poster Presentations
11th February 2012

CP1

Parents' Perspectives of Life Challenges Experienced by Long-Term Pediatric Brain Tumour Survivors: Preliminary Findings

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Pediatric brain tumour survivors (PBTS) are vulnerable to severe neurocognitive and psychosocial late effects. They appear to fare worse than other cancer survivors in terms of education, employment, and other social determinants of health. Because of these multiple challenges, PBTS are at risk for discrimination, and functional and financial difficulties in adulthood. Parents of PBTS witness the difficulties their children face as they transition to adulthood, and they usually play a substantial role supporting and advocating well into their child's adult years.

Objective: The objective of this pilot study was to begin to document parents' perspectives of the discrimination, and functional and financial difficulties experiences by young adult PBTS.

Materials & Method: Parents of PBTS are currently being recruited through the BC Cancer Agency Post-Pediatric Late Effects Clinic to complete an anonymous online survey.

Results: Preliminary analysis of 16 parents_ responses describes bullying (9/16) and discrimination experienced by PBTS at school (6/16) and work (5/16). Most PBTS cannot cover daily living expenses without parental support (11/16). Only one parent indicated their child's disability allowance covers their cost of living. Financial hardship was reported by 6 of the 11 families who pay for their child's medical expenses out of pocket. PBTS were also reported to have been the victim of theft, assault or fraud (5/16). The qualitative data provides vivid examples of these difficulties.

Conclusion: These findings suggest that some long-term PBTS experience previously undocumented significant life challenges which are poorly addressed by health and social programs.

CP2

Clinical evaluation of pineal parenchymal tumors - Hiroshima University Hospital Experiences

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The aim of this study was to evaluate the results of our hospital treatments for pineal parenchymal tumors (PPTs) which remain equivocal and controversial.

Patients and Methods: Twenty-two consecutive patients (12 males / 10 females, 13 adults / 6 children) with histologically proven PPTs were retrospectively reviewed. Follow-up periods were 3.3-272 (median 66) months (Ms).

Results: According to WHO 2000 classification, there were 10 pineoblastomas (PBs), 5 PPTs of intermediate differentiation (PPTsID), and 7 pineocytomas (PCs). In PBs group, tumors were totally removed in four, partially in three, and biopsied in three. Nine received cranio-spinal irradiation (CSI) except for one infant treated with surgery alone. Seven recently treated patients underwent platinum-based chemotherapy (PB-CTX) concurrently with CSI. Three with invasive lesions died early in follow-up period. Four remain alive and over-all survival time (OST) ranged from 27 to 125 (median 64) Ms. Of 5 PPTsID, four patients underwent gross total removal, and one partial removal. All received whole brain irradiation (WBI) with cone-down, three of whom underwent concurrent PB-CTX. Four remain alive and OST ranged from 34 to 272 (median 68) Ms. Tumor was totally removed in five of seven PCs cases, who received no adjuvant therapy. One with partially removed tumor underwent local field irradiation and gamma-knife therapy. Seventy-nine year-old male died with pneumonia 98 Ms after endoscopic biopsy only. Other six remain alive, and OST ranged from 14 to 253 (median 49) Ms.

Conclusions: First step to good outcome is gross total removal, because this allows patients with PC and PPTID to minimize the recurrence risk, and those with PB to give a plenty adjuvant treatment time without symptoms. Survey of QOL of long-term survivors and establishment of appropriate treatment for invasive PBs are urgent challenges. Randomized control trial will be a future issue to determine whether patients with PPTID should receive CS- or WB-/ local irradiation.

CP3

Elevated preoperative glucose levels and survival in elderly newly diagnosed glioblastoma patients

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This study was undertaken to assess the relationship between preoperative glucose level and survival in elderly patients with newly diagnosed glioblastoma (GBM).

Methods: We retrospectively reviewed 315 GBM patients e65 years. 18% (58/315) of the patients with known diabetes were excluded. The analysis was performed based on a recursive partitioning algorithm.

Results: 242 GBM patients with a median age of 74 yrs were included. Fifty-two percent were male. Twenty-three percent had a KPS of 90-100 preoperatively, in 44% KPS was 70-80, and 34% had KPS scores <70. 32% of patients underwent gross total resection, 25% subtotal resection, and 43% biopsy. Seventy-four percent underwent radiation therapy, and 43% had concurrent and/or adjuvant chemotherapy. Median preoperative glucose was 123 mg/dL (range 69-306). Median overall survival was 5.2 months. Patients were divided into four groups: group one (KPS>70, age<75 and preoperative glucose <90 mg/dL), group two (KPS >70, age <75, and preoperative glucose >90 mg/dL), group three (KPS>70, age>75, any glucose level), and group four (KPS<70, any age, any glucose level). Median survival times for patients in groups one, two, three, and four were 14.0, 7.9, 5.1, and 3.0 months, respectively. Those in groups two, three, and four were at progressively higher risk of dying (P <0.001).

Conclusion: In our study, higher preoperative glucose level was associated with decreased overall survival in elderly patients diagnosed with GBM. Strict glucose control may contribute to improved outcome in treatment of these patients.

CP4

The Canadian Virtual Brain Tumour Bank (CVBTB)

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The Canadian Virtual Brain Tumour Bank (CVBTB) is a national brain tumour banking resource that serves to further clinical, molecular and translational research. The CVBTB was created to provide research and academic communities easier access to high quality samples across the country. An informative, user-friendly and easy-to-navigate website, the CVBTB links brain tumour sample holdings from established brain tumour banks in Canada. As a virtual bank, the CVBTB does not store actual brain tumour samples but rather acts as a central point of access allowing researchers to query specific brain tumour samples. Once queries are completed, the CVBTB helps to coordinate the delivery of samples between researchers and respective tumour banks which includes the University of Toronto, London Health Sciences Centre, McGill University and the University of Calgary. The CVBTB also acts as a brain tumour banking resource by providing assistance on standardized operating procedures on procedures such as tissue sample accrual, tissue sample storage, blood and lymphocyte processing and tissue sample delivery. Under the collaboration of neurooncologists, ethics advisors, neuropathologists and technicians, the CVBTB hopes to play a large role in furthering brain tumour research and to make an impact both on a national and global scale.

For more information, please visit www.braintumourbank.ca or please contact: Takyee Tung/Jennifer Glen, CVBTB Coordinators, Nervous System Tissue Bank, University Health Network - Toronto Western Hospital ttung@uhnres.utoronto.ca/ jennifer.glen@uhn.on.ca

CP5

Hypofractionated radiotherapy (XRT) with or without concurrent temozolomide (TMZ) in elderly patients with glioblastoma multiforme (GBM): a review of ten-year single institutional experience

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We conducted a retrospective review of patients (age >60 years) treated with hypofractionated XRT at our institution between 2000 and 2010. We identified 112 patients who received hypofractionated XRT, with 57 receiving concurrent and adjuvant TMZ and 55 without concurrent chemotherapy. Of the 55 patients who received hypofractionated XRT alone initially, 24 subsequently received TMZ as salvage treatment at time of progression.

Results: Among the concurrent XRT+TMZ patients, mean age was 70 years (range 60-86), median KPS was 80 (range 30-100) and 24/57 (42%) received prior debulking surgery. Median overall survival (OS) among the XRT+TMZ patients was 6.9 months (95% CI, 4.5-8.6). Patients without concurrent chemotherapy were similar in demographics (age, sex, corticosteroid use, KPS) except 34/55 (62%) were debulked (p-value 0.045.) Median OS was 9.3 months (95% CI, 5.9-11.8) (p-value 0.351). Sub-group analysis revealed patients treated with initial hypofractionated radiation with salvage TMZ had increased median OS of 13.3 months (95% CI, 9.9-19.3) (p-value 0.012).

Conclusion: Our results suggest concurrent and adjuvant TMZ does not confer a survival benefit in elderly GBM patients. A sequential approach may be a more effective and efficient strategy by selecting responding patients who may benefit most from subsequent salvage chemotherapy.

CP6

Changes in functional abilities in high grade glioma patients undergoing initial treatment

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Individuals diagnosed with high grade gliomas are living longer because of advances in treatment. The benefits accrued from prolonged survival are tempered by the hardship of living with disability due to disease and treatment side effects. This study reports changes in cognitive status and self-reported functional abilities over time in a group of patients undergoing treatment for high grade gliomas.

Methods: Forty-three participants undergoing initial treatment for high grade gliomas were enrolled in this study. FACT-BR questionnaires, MoCA cognitive assessments, and patient and caregiver assessments of functional abilities are completed at regular intervals over one year. Semi-structures interviews explore the practical and functional challenges of a living with a brain tumour and identify strategies used by patients and their family caregivers to meet these challenges, and the extent to which these strategies are successful.

Results: Of the 43 enrolled study participants, 13 died or were deteriorating clinically before all assessments could be completed. Twenty-three patients (53%) met criteria for mild cognitive impairment at initial assessment. Nine participants are still completing assessments. Interim results of self-reports on changes in MoCA scores, functional abilities and FACT-Br scores will be presented.

Clinical Implications: This study will document the functional disabilities that are deemed important by brain tumour patients and their caregivers over time, as well as compensatory strategies they have used, and the gaps in care that persist. The data will be used in future care planning and intervention development.

CP7

Brain Tumor Support Groups: Patient and Caregiver Perspectives

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Most adult intra-axial tumours are incurable gliomas. Patients and their families benefit from comprehensive care that includes psychosocial support. Separate support groups for brain tumour patients and caregivers have been offered at our institution on a drop-in, monthly basis since 1999. Some people attend the group regularly but most families treated in our institution never attend. This qualitative study explored benefits and barriers to support group attendance through focus groups with patients and caregivers. Patient (n= 5) and caregiver (n = 8) attendees endorsed that separate groups provide an opportunity for frank discussion about the impact of the disease on their lives and they appreciated the open structure and format of the group design. Attendees identified that the group fostered universality and a place to obtain information. However, some participants described feeling isolated when their circumstances differed from others in the group. Patients who never attended the group (n=3) revealed a lack of knowledge about the purpose of the group and eligibility criteria. Barriers to group attendance included forgetting the date, and access to transportation or child care. Study findings indicate that people may be more likely to attend at key points along the illness trajectory (e.g. initial diagnosis, recurrence, palliation). We are surveying families who do not attend the groups in order to obtain additional information about their supportive care needs. These data will inform how the groups are facilitated in the future at our institution and may be used as a model for other neurooncology centres.

CP8

Patterns of failure in glioblastoma multiforme patients treated with accelerated hypofractionated, limited-margin external beam radiotherapy and temozolomide

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To evaluate the patterns of failure in patients treated with hypofractionated, limited-margin radiotherapy (hypo-IMRT) for GBM.

Methods: We reviewed the records of patients diagnosed with GBM who had radiological evidence of disease progression following treatment with hypo-IMRT and concurrent-adjuvant temozolomide. Patients received 60Gy in 20 fractions to the PTV60Gy defined as the GTV (residual T1-enhancing tumour and/or resection cavity) plus a median margin of 0.3cm (0 to 0.5cm) and 40Gy in 20 fractions to a PTV40Gy defined as the PTV60Gy plus a planned margin of 1.5cm (1.2cm to 2cm). Local recurrence was assessed by co-registering the treatment planning CT with the CT or MRI documenting disease recurrence. Patterns of failure were categorized as a function of their location relative to the planned dose regions. Toxicity was scored according to CTC v.4.

Results: Twenty-seven cases of recurrent disease in patients treated between 2004 and 2010 were available for review. Median follow-up was 11.2 months. Median time to recurrence was 7.0 months. Radiological evidence of tumour progression was demonstrated with CT in 5 patients and MRI in 22 patients. Twenty (74%) failed within the PTV60Gy, 1 (4%) failed within the PTV40Gy, 6 (22%) failed outside of the PTV40Gy with either multifocal disease (15%) or CSF dissemination (7%). Median time to recurrence was 7.1 months in those who failed within the high dose region and 4.2 months in those who failed out of the planned dose regions. There was no acute grade e3 radiation toxicity.

Conclusions: In patients treated with limited margin hypo-IMRT and temozolomide, 78% failed within planned dose regions and 22% had out of field failures. This is consistent with other published data.

CP9

A visual introduction to the adaptation of the pedicled flap in endoscopic reconstruction of the cranial base

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The transphenoidal approach provides a well-established route for ventral skull base surgery and in particular intrasellar pathology. The use of the vascular pedicled flap has effectively countered the complications previously associated with the bone and dural defect produced by this procedure. The purpose of this article is to introduce the reader to the various steps of this technique from a surgical perspective with the addition of an interactive video. Videos and still images obtained from 100 different endonasal endoscopic transphenoidal procedures, for standard sella pathology and expanded approach for parasellar and anterior fossa tumors were used and edited to create step-by-step interactive videos of surgical approach and its surgical nuances. Teaching of endoscopic techniques is challenging and simulation models are not readily available at most institutions. We believe the implementation of this video provides a greater insight to the technique and provides an invaluable education tool for residents, fellows and neurosurgeons who wish to acquire this technique and approach.

CP10

Radiation therapy for clinical hormonally-active pituitary adenomas: efficacy and safety

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Radiation therapy (RT) plays an important role in treatment of pituitary tumors that are resistant to medical and surgical therapy. The continuous development in the field of RT warrants a reassessment of its role as either initial or adjuvant therapy in the treatment of pituitary tumors and the adverse effects of this treatment.

Objective: The purpose of this study is to assess the outcome of RT as observed in the treatment of hormonally-active and inactive pituitary adenomas. An emphasis is placed on identifying potential prognostic factors, determining the control rate after radiation and evaluating late toxicity.

Methods: From 1997 to 2010, 125 patients with pituitary adenomas received RT, 35 of which were hormonally-active pituitary adenomas. The median age was 52 (range 28-79), with 21 females and 14 males for the hormonally-active patients. There were 18 patients with growth hormone secreting, 5 prolactinoma and 12 with Cushing's disease. The median follow-up was 2.2 years. Tumor control was defined as normalization of basal hormone level and lack of progression of adenoma assessed by imaging studies. The variables assessed for tumor control

were: age, sex, tumor type, tumor extension, radiation dose and radiation field size.

Results: Radiotherapy resulted in stable outcome in 95% of patients with inactive pituitary adenomas. Stable outcome was seen in 74% of hormonally-active patients with 24% not requiring any further drug therapy. Hypopitutiarism in one or more axis was observed in 52% of the cases with inactive pituitary adenomas and 29% of the cases with hormonally-active disease. One patient died due to development of pituitary carcinoma. Cause-specific survival rate were 97% during the course of the study. None of the prognostic factors for tumor control were found to be significant. On univariate and multivariate analysis none of the factors investigated where identified as predictors of response to RT.

Conclusion: Post-operative RT is indeed effective in gaining tumor control and thus nullifying the space-occupying effects of hormonally active pituitary adenomas. However, RT falls short in the sphere of biochemical control, which is observed in less than half of the cohort in our study. In terms of acute and late effects of RT, data from our study supports the previously well documented adverse effects, with new-onset hypopituitarism as the most frequent complication. No patient experienced radiation optic neuropathy or CNS malignancy in the field of radiation. No predictors of adverse radiation effects were identified.

CP11

Does pretreatment growth rate of vestibular schwannomas predict response to radiosurgery and adverse radiation effects?

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Stereotactic radiosurgery (SRS) is a well-established treatment option for vestibular schwannomas (VS). We examined whether pre-treatment tumor growth rate (TGR) predicts pattern of growth response to SRS and is a determinant of adverse radiation effects (ARE).

Methodology: All VS patients treated at our institution between December 2005 to 2011 using Model 4C Gamma Knife Unit were reviewed. Patients with clinical and radiological follow-up at least 12 months before and after SRS were selected. Tumor volume was determined from T1-weighted and FIESTA MRI scans obtained at every six-month intervals (pre- and post-SRS) using the ITK-SNAP software.

Results: Mean growth rate pre-SRS was +94.6%/year, and post-SRS was -10.8%/year. We classified tumors into three categories based on volumetric growth rate: class I (<52%), class II (52%_73%), and class III (>73%). We did not find a direct correlation between pre- and post-treatment TGR ($p>0.40$). A significant correlation was found between pre-treatment TGR and the extent of reduction in TGR post-SRS ($p<0.001$). 33% of VS patients treated GKRS experienced non-auditory ARE. Pre-treatment growth rate did not correlate with the occurrence of any ARE. Post-treatment TGR was a predictor of facial nerve dysfunction.

Conclusion: Tumors with greatest pre-treatment growth rate had the most favorable response to SRS. TGR pre-SRS did not predict ARE, though target volume predicted facial nerve dysfunction. Response patterns to SRS can be categorized into three classes. These results demonstrate that there are clearly different subtypes of vestibular schwannomas that need further molecular profiling and correlative molecular imaging to be able to guide treatment decision.

CP12

Multidisciplinary assessment of fitness to drive in brain tumour patients: a gray matter

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Physical and neurocognitive deficits from brain tumours may impair the ability to drive. While guidelines exist to inform when patients should be reported to licensing authorities as unfit to drive, physicians often find it challenging to assess driving ability.

Methods: Physicians from disciplines involved in the management of brain tumours in South-western Ontario were identified through the College of Physicians and Surgeons of Ontario database and surveyed by mail. Responses were analyzed for demographics, opinions, and factors influencing the decision to report. Fisher's exact test was performed to determine significant differences in responses between specialists and family physicians.

Results: A total of 467 surveys were distributed with 198 (43%) responding. Most respondents (76%) felt that reporting guidelines were unclear. Neurologists (43%), medical oncologists (34%), followed by family physicians (22%) were felt to be the most responsible physicians to report unfit drivers. When compared to specialists, family physicians were less likely: to be comfortable with reporting ($p=0.02$), to consider reporting ($p<0.001$), to inquire about patient's driving ($p<0.001$) and to discuss the implications of driving ($p<0.001$). Perceived barriers in assessing fitness to drive included: lack of tools to assess (57%), negative impact on patient-physician relationship (34%), unclear requirements to report (24%), and lack of time to assess (20%).

Conclusion: The assessment of fitness to drive in patients with brain tumours remains a challenge even in the multidisciplinary setting. There is a lack of consensus on which specialty is most responsible to assess and report medically unfit drivers.

CP13

Driving fitness of patients with brain tumours: reporting practices of physicians

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In most Canadian jurisdictions, there is a legal requirement to report medically unfit drivers. While seizures are clear grounds for cessation of driving, other deficits from brain tumours may also impair driving ability. We thus reviewed our institution's experience in evaluating fitness to drive in these patients.

Methods: Patients receiving brain radiotherapy at the London Regional Cancer Program between January to June 2009 were identified via our institutional database. In addition to descriptive statistics, details of driving assessment were reviewed retrospectively. Fisher's exact test was performed to determine factors predictive of reporting a patient as unfit to drive. A logistic regression model was constructed to further predict for factors predictive of reporting.

Results: A total of 158 patients were available for analysis after excluding 21 patients (n=17 prophylactic cranial irradiation, n=4 ineligible to drive). Forty-eight patients (30%) were reported to the ministry of transportation, and 64 (41%) were advised not to drive. Of the 53 patients with seizures, 36 (68%) had a documented discussion on driving, but only 30 (56%) were reported to the ministry. Age, primary disease, previous neurosurgery and the presence of seizures were predictive of reporting on Fisher's exact test ($p<0.05$). The presence of seizures (OR 12.4) and primary CNS disease (OR 15.5) were predictive of reporting on logistic regression modeling.

Conclusion: The implications of driving for brain tumour patients are not routinely discussed and/or documented. Despite guidelines and laws, there is absence of documentation of reporting for patients with seizures, suggesting a risk that some may have gone unreported altogether.

CP14

Two Cases of Cystic Meningioma: An Unusual Clinical Entity

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Cystic benign meningiomas account for only a small percentage of meningioma overall. They usually have a complex radiographic appearance that may suggest a higher grade meningioma or even another brain tumor type.

Case Reports: The first case is that of a 57-year-old woman who was found to have an incidental right frontal lesion radiographically consistent with a benign meningioma. A tumor cyst was noted at the four year radiographic follow-up. The cyst was larger at five years and she had developed simple partial seizures. She underwent resection and pathology revealed a WHO grade 1 meningioma. The second case is that of a 49-year-old woman who presented with progressive left sided weakness. Neuroimaging revealed a right frontal parasagittal cystic mass that was radiographically concerning for a high-grade glioma. She underwent resection and pathology revealed a WHO grade 1 meningioma. Symptoms improved in both patients and they both remain free of radiographic tumor progression.

Discussion: Cystic benign meningiomas represent only 2-4% of meningiomas. Given that they may have a complex, heterogeneous appearance on neuroimaging, they may be difficult to distinguish from higher grade meningiomas or other types of malignant brain tumor. Surgery may be necessary to establish a diagnosis, especially in symptomatic patients.

CP15

Thyroid Metastasis to an Anaplastic Meningioma: Case Report

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Tumor-to-tumor metastases are uncommon. The most common types of recipient tumor are renal cell carcinoma and sarcoma. The most common types of donor tumor are breast and lung. We report the case of a thyroid carcinoma metastatic to an intracranial anaplastic meningioma.

Case Report: A 64-year-old woman was diagnosed with papillary thyroid cancer three years prior to this presentation. She was treated with a total thyroidectomy, neck dissection, and radioactive iodine. One year later a follow-up CT scan revealed lymphadenopathy and she underwent a modified neck dissection and a second treatment with radioactive iodine. More recently MR imaging of the head revealed a right parietal extra-axial lesion extending into the scalp. She underwent craniotomy and pathology revealed both thyroid carcinoma and anaplastic meningioma. Despite further radiation therapy, follow-up MR imaging showed recurrent tumor and she underwent repeat craniotomy for tumor resection. She is currently receiving post-operative radiation.

Discussion: This case demonstrates a thyroid papillary carcinoma metastatic to an intracranial anaplastic meningioma. Thyroid metastases are rare with only a few cases reported in the literature. Previous case series have shown meningiomas to be the third most common type of recipient tumor for tumor-to-tumor metastasis. The aggressive nature of the lesion in this patient may be explained by the nature of both the donor tumor and the recipient tumor.

CP16

Glioblastoma in the Elderly: The Cleveland Clinic experience (1991-2010)

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Glioblastoma (GBM) is the most common malignant primary brain tumor. About 50% of cases occur in patients >65 years, however there is limited data on prognostic factors in these patients.

Methods: After IRB approval, the Cleveland Clinic Brain Tumor and Neuro-Oncology Centre's database was used to identify histologically confirmed GBM patients >65 years at the time of diagnosis. Multivariable analysis was conducted to identify independent predictors of survival using a Cox proportional hazards model and a stepwise selection algorithm with p=.05 as criteria for entry and retention.

Results: 512 GBM patients with a median age of 73 years (range 65-91, 54% male) were included. Forty-four percent of patients had biopsy only, 29% had gross-total-resection, 6% had near-total-resection and 21% had subtotal-resection. Seventy percent of patients underwent radiation, 34% had concurrent chemotherapy (CT), and 22% had adjuvant CT. Ninety-percent of patients had died at the time of analysis. Median overall survival was 6.3 months (95% C.I. 541-6.9); one year survival was 24% + 2%. On multivariable analysis, five factors were identified as independent predictors of overall survival: age at diagnosis (p<.0001), extent of resection (p<.0001), multifocal disease (p=.0008), seizure at presentation (p=.02), and Performance Status (p<.0001).

Conclusions: As seen in younger GBM patients, advancing age, performance status and extent of tumor resection were found to be independent prognostic factors. In addition seizure at presentation was associated with better outcome and multifocal disease had worse prognosis.

CP17

WHO grade III gliomas

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Anaplastic astrocytoma (AA), anaplastic oligodendroglioma (AO), and anaplastic oligoastrocytoma (AOA) are the major histological types of WHO-grade-III-gliomas. Most randomized trials pool both grades III or IV gliomas in their analysis. Consequently, there is limited data on prognostic factors for patients with grade III gliomas.

Methods: After IRB approval, institute's database was used to identify grade III glioma at diagnosis. Multivariable analysis was conducted to identify independent predictors of survival using a Cox proportional hazards model and a stepwise selection algorithm with p less than .10 as criteria for entry and p less than .05 for retention.

Results: 336 patients with median age of 50 years (range, 1-88 years, 52 percent-men) diagnosed between 1994 and 2009 were included. Forty-nine percent had biopsy, 21 percent had gross total resection (GTR), 5 percent had near total resection (NTR), and 25 percent had subtotal resection (STR). Ninety-two percent of patients underwent radiation and 62 percent underwent concurrent chemotherapy. Median overall-survival of AA, AOA, AO was 17.0 months, 58.7 months and 74.2 months respectively. Five factors were identified as independent predictors of overall survival, age at diagnosis, Performance Status, histology, multifocal disease and type of surgery.

Conclusion: Older age, poor performance status, AA or AOA histology, and multifocal disease were associated with higher mortality. GTR or STR, relative to biopsy, was associated with lower mortality.

CP18

Extracranial extension of glioblastoma with concomitant dedifferentiation – A case report

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A rare case of glioblastoma with local scalp extension and S-100 immunonegativity is presented in a 63-year-old man. Magnetic resonance imaging at initial presentation revealed a right fronto-parietal mass, diagnosed as glioblastoma following stereotactic biopsy. The patient declined treatment with chemotherapy and radiation. Seven months later, the patient presented with an enlarging mass adjacent to the site of craniotomy contiguous with intracranial tumour through the bone flap. The patient underwent repeat craniotomy and gross total resection of the tumour. Histopathology was consistent with glioblastoma. Immunohistochemistry was negative for both GFAP and S-100. Despite a highly aggressive course, extradural extension of glioblastoma is exceedingly rare. This case appears to be the first reported scalp extension of glioblastoma. This case does not appear to be scalp metastases based on radiological findings. A discussion on the mechanism of extradural extension is presented with molecular findings.

CP19

Stereotactic Radiosurgery of Brain Metastases in Elderly Patients

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Elderly patients often suffer from cerebrovascular impairment. Whole brain radiotherapy (WBRT) can cause vascular damage and enhances the risk of dementia. For patients

with a limited number of brain metastases (BM) stereotactic radiosurgery (SRS) is promising alternative.

Methods: After IRB approval, institute's database was used to identify BM patients greater than 70 years at diagnosis and underwent SRS between 2000-2009. Multivariable analysis was conducted to identify predictors of survival using a Cox proportional hazards model and stepwise selection algorithm with p equal to 0.10 and p equal to 0.05 as criteria for entry and retention.

Results: 173 BM patients with a median age of 75 years (range 70-87, 64 percent male) were included. Most patients had lung-cancer (55 percent) or kidney-cancer (16 percent) and the median time between diagnosis of the primary cancer and BM was 10.3 months (0-309.6 months). Median overall survival (OS) was 5.5 months from the time of SRS (95 percent CI, 4.4-7.2 months). Cause of death was extracranial tumor progression in 35 percent, cerebral tumor progression in 3 percent, both cranial and extracranial progression in 9 percent, and unknown in 53 percent.

Conclusion: On multivariable analysis, performance status, interval from diagnosis of the primary cancer to BM, WBRT prior to SRS and lack of extracranial metastasis are independent predictors of OS.

CP20

Prognostic Factors in Adult Medulloblastoma

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Purpose: We report on prognostic factors for survival and recurrence in adult medulloblastoma patients at two institutions.

Materials/Methods: The charts of 71 consecutive patients between 1944 and 2008 were reviewed. Univariate and multivariate analysis using the Cox regression model and logistic regression analysis was performed.

Results: Median age of the 48 male and 23 female patients was 27 years (age range, 16-71 years). By Children's Oncology Group risk stratification 15 patients (21%) were poor risk, 38 patients (54%) standard risk, and 15 patients (21%) unknown. 66 patients received radiotherapy and of these 63 patients received craniospinal radiotherapy (CSI). Thirty-eight (48%) patients received chemotherapy at some point in their treatment (7 concurrent, 31 after recurrence). Median survival from diagnosis was 4.4 years (range 0-20 years). In univariate analysis diagnosis after 1990 ($p = 0.007$) and female gender ($p = 0.039$) predicted for decreased rates of recurrence. A trend for subtotal resection predicting for increased rates of spinal recurrence was evident ($p = 0.083$). CSI and posterior fossa boost were prognostic for both decreased recurrence ($p = 0.041$ (fossa boost), $p = 0.0$ (CSI) and improved survival ($p = 0.047$ (fossa boost), $p= 0.0$ (CSI)). Chemotherapy was prognostic for decreased recurrence ($p = 0.025$).

Conclusions: High rates of local and spinal recurrence is a significant issue in adult medulloblastoma. Subtotal resection resulted in a trend towards increased rates of spinal recurrence. CSI and posterior fossa boost were prognostic for both decreased recurrence and increased survival. Chemotherapy was prognostic for decreased recurrence.

CP21

The outcome of supratentorial ependymoma diagnosed in infancy: a Canadian experience

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Introduction: Supratentorial ependymoma (STE) in infancy is uncommon. Infancy has been reported as a poor prognostic factor in ependymoma. We postulated that STE in infancy is more benign than posterior fossa ependymoma (PFE).

Methods: We performed a retrospective review of children diagnosed with STE in 12 Canadian centers, between 1986 and 2006. The clinical data was acquired through standardized data forms, and chart review. Central review of pathology was performed.

Results: Age under three years was not identified as a poor prognostic factor among the 51 patients diagnosed with STE. STE represented 13% of children with ependymoma diagnosed in infancy. 60% of the infants with STE are survivors median 10yrs (0.8-11); 40% of posterior fossa ependymomas are alive median 8 yrs (2-17). STE: median age 2.3 mos (0.4-2.8); 60% male; 70% WHO grade 2. Deficits of survivors: 1 hearing; 1 motor. 9/10 had a gross total resection (GTR >95%), 4 received adjuvant therapy (1 XRT + chemo, 3 chemo) at diagnosis. One child was salvaged at relapse with GTR, chemotherapy, then XRT. The child with dissemination died. Other deaths: secondary GBM in XRT field; multifocal disease post XRT; septic shock.

Conclusion: Thirteen percent of ependymomas diagnosed before age three are STE. Leptomeningeal and multifocal disease are poor prognostic features. The prognosis of STE in infancy is superior to those arising from the posterior fossa. GTR is the mainstay of therapy, future studies identifying biological markers may assist in determining which STE require adjuvant therapy.

CP22

Self reported neurocognitive concerns in relation to tumor location in adults with glioblastoma multiforme

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Neurocognitive problems frequently occur following a brain tumor. We examined self-reported neurocognitive difficulties in 34 adults (26-74 years old; mean SD: 53.1 12.0) diagnosed with GBM using the Neurocognitive Questionnaire (NCQ). The NCQ monitors functioning across four domains: Task-Efficiency, Emotional-Regulation, Memory, and Organization. NCQ scores were converted to z-scores according to population norms and comparisons were made based on tumor location and hemisphere using one-sample t-tests and ANOVA. Compared to population norms, patients with frontal lobe tumors endorsed more Task-Efficiency and Memory complaints (Right, Task-Efficiency: -1.50 1.62, Memory: -0.90 1.00; Left, Task-Efficiency: -1.12 1.50, Memory: -1.25 1.41). In contrast, patients with right and left temporal lobe tumors endorsed fewer problems with Emotional-Regulation (0.56 0.66, p=0.04) and Organization (0.74 0.34), respectively. Notably, self-reported memory problems in temporal lobe patients were not different from population norms. When comparisons were made between groups, patients with right hemisphere tumors reported more Organization problems (main effect of hemisphere; F(1,30)= 10.16, p=0.003). Patients with frontal lobe tumors tended to report more Task-Efficiency and Emotional-Regulation problems than did patients with temporal lobe tumors, although the effect of tumor location did not reach statistical significance (Task-Efficiency: F(1,30)=3.60, p=0.07; Emotional-Regulation: F(1,30)=3.49, p=0.07). These results suggest that tumor location is associated with specific self-reported neurocognitive problems that are not necessarily the same as would be expected based on objective neurocognitive testing. To better understand issues of sensitivity and specificity of self-report questionnaires, we are exploring the relations between tumor factors (location, treatment, stage of illness), adjustment (illness intrusiveness, depression), neurocognitive complaints, and objective measures of performance.