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THE GFAP GENE IS METHYLATED IN GFAP-NEGATIVE HUMAN ASTROCYTOMAS.

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Glial fibrillary acidic protein (GFAP) is an intermediate filament specifically expressed in glial cells which contributes to and maintains the stability of the astrocyte's cytoskeleton. We have previously observed that GFAP expression is reduced in malignant glial tumors, and that the up-regulation of GFAP expression affects glial cell proliferation and tumorigenicity (Cancer Res. 53:3624, 1993). To determine how the transcription of the GFAP is repressed in malignant glial tumors, we looked for genomic rearrangements of the GFAP gene by Southern analysis, but none was found. However, we have shown for the first time that the GFAP gene was hyper-methylated in five GFAP negative glioma cells. This hyper-methylation was also detected in other GFAP negative non-glial cells. Both hyper- and hypo-methylation of DNA have been shown in a variety of tumor types to be important factors affecting gene transcription. This methylation-mediated repression of transcription is thought to be a candidate mechanism for the decreased expression of several tumor suppressor genes, and may also be one mechanism by which there is loss of GFAP gene expression in malignant gliomas (Supported by NCI Canada).

REGULATION OF PROTEOLYTIC ACTIVITY RELEASED BY C6 ASTROCYTOMA CELLS.

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Background: Tumor cells regulate extracellular proteolytic activity both by inhibitors and activating molecules. The ratio between these regulator molecules and the level of proteases determines whether the vascular membrane will be degraded for the initiation of angiogenesis. Levels of collagenase IV activating factor (CAF) were assessed in media conditioned by a rat glioma cell line (C6) and a human glioma cell line (U251). To develop a mechanism for activation of proteases, CAF was compared to activation by the Endothelial Cell Stimulating Angiogenesis Factor (ESAF).
Methods: C6 and U251 were grown in serum free conditioned media. Procollagenase IV obtained from U251 media was used to assay the levels of CAF in the media of the two cell lines. ^3H collagen IV was utilized to assay collagenase IV activity.
Results: Total basal collagenase IV activity of C6 astrocytoma cells was 4X greater than U251 cells. C6 conditioned media contained 10X greater levels of the collagenase IV activating factor compared to the U251 media. Addition of either CAF or ESAF increased the total basal collagenase IV activity of U251 by 5X and 4X respectively, to comparable levels of basal C6 collagenase IV activity. Neither factor effected the total C6 collagenase IV activity.
Conclusions: CAF appears to be characteristic of an ESAF-like molecule. C6 cells represent a rich source of CAF. In the human glioma cell line, collagenase IV activity appears to be under stricter control than in the rat counterpart. The lower levels of CAF from U251 cells suggests that in certain human tumors an alternate mechanism may exist for activating collagenase IV in vivo.

THE UP-REGULATION OF TIMP-1 IN HUMAN ASTROCYTOMA CELLS DECREASES ASTROCYTOMA INVASIVENESS

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We have previously shown that the imbalance between the level of type IV collagenases and their corresponding inhibitors (TIMPs) may be essential steps in the invasiveness of human malignant astrocytomas. Furthermore, we have shown that the more differentiated, less anaplastic astrocytomas express higher transcripts for TIMP-1 and TIMP-2 than do highly anaplastic astrocytomas. To determine if up-regulation of TIMP genes and gene products could modulate the invasiveness of human malignant astrocytoma cells, in the present study we have transfected a highly invasive astrocytoma cell line, SF-188, with an expression vector carrying a full-length TIMP-1 cDNA. Typically, SF-188 overexpresses the 72- and 92-kDa type IV collagenases with little expression of TIMP-1. Following transfection, SF-188 astrocytoma cells overexpressed the TIMP-1 transcript and secreted lesser amounts of the type IV collagenases than did controls. The stable TIMP-1 SF-188 transformants demonstrated marked morphological changes and diminished growth rates in soft agar when compared to controls. The invasiveness of successfully TIMP-1-transfected astrocytoma cells across matrigel-coated filters was significantly decreased over controls. These results suggest that up-regulation of TIMP-1 in SF-188 astrocytoma cells has directly decreased their invasive potential. Supported by NCI (Canada).

THE ROLE OF CAI, A NOVEL SIGNAL TRANSDUCTION INHIBITOR IN THE CONTROL OF GLIOMA CELL INVASION *IN VITRO*.

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The invasiveness of human glial tumors results in infiltrative growth and progressive regional metastases, recurrence with local treatment failure, malignant progression and the death of the patient. Anti-proliferative therapy with radiation and chemotherapy have impacted the clinical natural history only minimally. The designation of invasion as a therapeutic target as such is unique and is intended to restrain the regional migration of tumor cells, allowing local therapy to be more effective. We have used the agent CAI (carboxyamido-triazole), identified by means of its anti-migration activity in systemic tumor cells and applied it in a model of glioma tumor invasion. This drug is an inhibitor of G-protein-mediated signal transduction and interferes with cellular calcium influx, inhibiting downstream calcium-dependent events, including the release of arachadonic acid and tyrosine phosphorylation. The Matrigel™ barrier assay, in which cells are placed in a chemoattractant gradient with a coated filter barrier and the migrating cells are counted, does not represent the extracellular matrix of the brain as such, but provides a means of impeding the cells enough to measure invasive capacity. CAI in concentrations of 2-20 μM inhibits glioma migration by an average of 60% in 9 of 10 cell lines tested. Cytotoxic/static effects on cells at these concentrations reduce cell numbers from 0-20% only, suggesting specific anti-invasive activity. We are currently using this agent in glioma xenografted animals with serial MR imaging and segmentation of the invasion front for volumetric quantitation.

PDGF Dominant-Negative Mutants Decreases Malignant Astrocytoma Cell Growth: Abhijit Guha[1], Steve Shamah[2] & Charles Stiles[2]. 1-Div. of Neurosurgery, Univ. of Toronto. 2-Dana-Farber Cancer Inst., Boston

Expression of PDGF ligand (PDGF-A & B) and receptors (a & b) by malignant astrocytomas suggests PDGF autocrine stimulated growth. A PDGF dominant-negative mutant (DNM) was made by altering a cysteine residue involved in intramolecular folding of PDGF-A. This DNM could heterodimerize to both PDGF-A & B and prevent formation of any functional dimeric PDGF. Fibroblasts transformed by overexpression of PDGF-A or B when transfected with the DNM, reverted towards normal growth. We now report the ability of this PDGF DNM to decrease the tumorgenic growth of human glioblastoma cell lines.
The PDGF DNM was cloned into pLNCX vector under control of the CMV promoter and transfected into U-343 Mg Cl2:6 and U-87 cells. Stable pooled colonies were obtained using G418 selection. RNA protection assay confirmed DNM mRNA expression. Autocrine activation of PDGF receptors, demonstrated by western analysis with anti-phosphotyrosine antibody, was decreased in the cells expressing the DNM and not in control cells. These DNM expressing cells grew at a slower rate, were serum dependent and showed decreased colony and focus formation. The astrocytoma lines were injected into nude mice to determine their in-vivo growth. There was decreased tumor formation in animals injected with the DNM expressing astrocytoma cells. Longterm goal of using the PDGF DNM in gene therapy of malignant astrocytomas are planned.

PROTEIN KINASE C REGULATES GLIOMA GROWTH, V.W. Yong, N.P. Dooley, G. Baltuch, M. Rostworowski, J.G. Villemure, Montreal Neurological Institute, McGill University, Montreal.

Following from observations in this laboratory that the proliferation rate of non-malignant human or rodent astrocytes is dependent on cellular protein kinase C (PKC) enzyme activity, we have examined the role of PKC in glioma growth in vitro. We have found that 1) human or rat glioma cells contain high PKC enzyme activity which correlates with their rapid growth rate, 2) inhibitors of PKC (staurosporine, tamoxifen and CGP 41251) block the proliferation rate of human or rat glioma cells, at IC50 values that correspond to their respective IC50's for inhibition of PKC activity, 3) of the calcium-dependent PKC isoforms, human glioma cells contain α but not β or γ, while rat glioma cells express α and β but not γ, 4) of the calcium-independent isozymes analysed, both rat and human glioma cells contain δ, ε and ζ, 5) of the expressed isoforms, the activity and amounts of PKCα correlate with cellular growth, and 6) an antisense oligonucleotide directed against PKCα decreases the proliferation rate of glioma cells. Current experiments are aimed at discerning the effects of PKC inhibitors (particularly tamoxifen, which is clinically useful in some glioma patients) in regulating PKC isozymes expression. We suggest that aberrations of the PKC signal transduction system, particularly of PKC α, are important factors in the transformation and growth of glioma cells.

ANTISENSE OLIGONUCLEOTIDES TO PROTEIN KINASE C (PKC) α AFFECT PROLIFERATION AND *RAS* EXPRESSION IN GLIOMA CELL LINES. N.P. Dooley, G.H. Baltuch, M. Rostworowski, J.-G. Villemure, and V.W. Yong. McGill University.

Numerous studies have demonstrated an important role for the protein kinase C family of enzymes in the initiation and progression of the malignant phenotype. Previous reports from our laboratory have shown that phosphorothioate antisense oligonucleotides directed against the site of initiation of translation of PKC α inhibit proliferation of human (A172) and rat (C6) glioma cell lines, when compared to sister cultures which were either untreated or treated with randomly generated control oligonucleotides. In human glioma lines, a 25% decrease in the level of PKC α expression, as determined by I^{125} Western blotting, resulted in a 50% decrease in tumor proliferation *in vitro*. Similarly, in rat glioma cell lines, a 40% decrease in PKC α levels, effected a 60% decrease in cell growth. Using a histone phosphorylation assay, the total PKC activity was found to be significantly decreased when compared to controls in both antisense treated rat and human glioma cell lines. The specificity of this inhibition of tumor growth was not the result of a generalized cytotoxicity, as determined by lactate dehydrogenase assays. Preliminary results in C6 glioma cell lines demonstrate that *ras* expression in antisense treated cultures is increased by over 25% when compared to controls. These findings suggest that the expression of PKC α and *ras* is inter-related in glioma cell lines. A better understanding of the role of protein kinase C in the transduction of proliferative signalling may have significant implications for future therapeutic strategies in the treatment of gliomas.

PROTEIN KINASE C INHIBITORS INDUCE APOPTOSIS IN HUMAN ESTABLISHED GLIOMA CELL LINES. W.T. Couldwell, D.R. Hinton, M.H. Weiss, R. Law. University of Southern California, Los Angeles, CA

Previous work has demonstrated an important role of the Protein Kinase C (PKC) system in regulating glioma growth, and has led to clinical trials utilizing PKC inhibitors as adjuncts in the therapy of patients harboring malignant gliomas. In this regard, clinical use of high-dose Tamoxifen in patients with malignant gliomas has indicated that some patients demonstrate tumor regression, which is surprising considering the expected cytostatic nature of the treatment. The present study was performed to explore the possibility that inhibition of PKC in these tumors was triggering an *apoptosis* (i.e. programmed cell death) signal. Glioma cell lines A172 and U87 were grown in tissue culture and treated for various periods (3-7 days) with the PKC inhibitors Staurosporine (10 nM) and Tamoxifen (10 μM). Cells were harvested, and purified DNA was analyzed by agarose gel electrophoresis. As a positive control, cells were treated with 100 ng/ml TNF-α to induce apoptosis. DNA from cells treated with either staurosporine or TNF-α exhibited a classical "ladder" pattern of oligonucleosome-sized fragments characteristic of apoptosis during the 3-7 day treatment period. Tamoxifen produced a similar result, although the DNA ladder was less pronounced. No oligosomal DNA fragments were detected in cells deprived of growth factors for seven days in serum-free medium, indicating that merely inhibiting the cell proliferation signal from growth factors was insufficient to induce apoptosis. These observations indicate that the *in vitro* treatment of glioma lines with PKC inhibitors induces programmed cell death; the important clinical implication of this observation being that this type of therapy may in fact kill tumor cells rather than merely inhibiting their growth.

PROTEIN KINASE C AND GROWTH REGULATION OF PITUITARY ADENOMAS. William T. Couldwell, David R. Hinton, Ron Law, Martin H. Weiss. Department of Neurological Surgery, University of Southern California, Los Angeles, CA

Previous work has demonstrated an important role of the Protein Kinase C (PKC) signal transduction system in regulating glioma growth; malignant gliomas express very high PKC activity which correlates strongly with their proliferation rates *in vitro*. These observations have led to clinical trials utilizing PKC inhibitors as adjuncts in the therapy of patients harboring malignant gliomas. To explore the role of the PKC system in growth regulation of **pituitary adenomas**, primary tumor cultures were plated from fresh surgical tumor specimens. PKC inhibitors Staurosporine and Tamoxifen were added to the cultures; measurements of cell proliferation were performed by [^{3}H]-thymidine uptake and the MTT assay. After a 48 hour period, cells were harvested for the proliferation assays; both [^{3}H]-thymidine uptake and absorbance on the MTT assay decreased in a dose-related manner in both the staurosporine and tamoxifen-treated cultures (IC_{50} of 10 nM and 30 μM respectively). Direct measurement of PKC activity using an *in vitro* assay revealed very high activity (range of 1465-5708 pmol/min/mg protein; within the range recorded for malignant glioma specimens) in 12 frozen specimens of pituitary adenomas (8 nonfunctional adenomas, 3 prolactinomas and 1 corticotroph-secreting adenoma) and 2 established pituitary adenoma lines. An isozyme-specific assay indicates the majority of this activity is related to the α-isozyme. These preliminary data indicate that pituitary adenoma cells display high PKC activity and are sensitive to growth inhibition by PKC inhibitors. These data suggest a role for the PKC system in regulating pituitary tumor growth, which may have implications for future therapy of these tumors.

CYCLIN GENE EXPRESSION IN HUMAN ASTROCYTOMA CELL LINES Dirks PB, Hubbard SL, Fukuyama K, Matsuzawa K, Rutka JT., Brain Tumor Research Laboratory, Hospital for Sick Children, University of Toronto

Derangements in cell cycle gene expression have been found in a variety of human cancers. Malignant astrocytomas are aggressive neoplasms which are characterized by rapid proliferation. To determine if astrocytoma cell proliferation correlates with alterations in cyclin gene expression, we performed northern blot analyses to study cyclin gene transcripts in seven malignant human astrocytoma cell lines using molecular cDNA probes to cyclins A,B,C,D1, D3, E. In our analysis of astrocytoma cell lines, cyclin B was overexpressed in U 87 MG and U 343 MG-A; cyclin C was overexpressed in SF 188 and U 343 MG-A; cyclin D3 was overexpressed by SF-188 and U 87 MG; cyclin D1 was overexpressed in SF-126, U 343 MG-A and XF-498; and cyclin E was overexpressed in U 251 MG and XF-498. There were no aberrant sized transcripts for any of the cyclin genes in any of the astrocytoma cell lines studied. Comparisons of cyclin gene expression in astrocytoma cell lines were referenced to cultures of normal human brain or cultures of normal human fibroblasts in early passage.. Our results suggest that overexpression of cyclin gene transcripts is frequently seen in human astrocytoma cell lines, but that there is variable expression of different cyclin transcripts for each of these tumors. We are currently extending our observations to include the analysis of cyclin genes in synchronized astrocytoma cells in culture, and in astrocytoma specimens of varying grade malignancy to further understand the role that these cell cycle genes may play in astrocytomas.

IMMUNOHISTOCHEMICAL ANALYSIS OF ESTRAMUSTINE BINDING PROTEIN IN ASTROCYTES AND GLIOBLASTOMA. J. M. Piepmeier, P. E. Pedersen, C. A. Greer Yale University Neuro-oncology Laboratory, New Haven, Connecticut, USA

Estramustine, a potent antiproliferative agent on malignant gliomas, accumulates within cells containing estramustine binding protein (EMBP). Antisera raised against EMBP recognizes an antigen that is expressed in human glioma tissue, however a detailed analysis of the topographical localization of this binding site has not been published. We performed an immunohistochemical analysis (DAB, ABC kit) with antisera raised against EMBP (B. Hartley-Asp, Helsingborg, Sweden) to examine its location and relative concentration in 3 human glioblastomas (HS683, J889H, H1289G) as well as human astrocytes. In each culture staining was noted to be relatively concentrated around the nucleus and in a parallel array of fibers suggesting an association between EMBP and the cytoskeleton. Because estramustine has been shown to act as an antimicrotubule agent in human gliomas, we examined the spatial relationship between EMBP and microtubules, by double labeling 3 tumors and astrocytes with anti-ß tubulin (fluorescein secondary antibody) as well as anti-EMBP (Texas Red secondary antibody). Staining patterns were examined by Confocal microscopy. There were striking similarities in the pattern and distribution of both EMBP and microtubules. Both anti-ß tubulin and anti-EMBP labeled a delicate network of fibers extending from the nucleus into virtually all cell processes with focal accumulation in terminal growth cones. However, staining patterns were not identical. EMBP appeared more concentrated around the nucleus and was less discrete. Our data suggest that EMBP not only is associated with microtubules, but also may have a secretory function. Previous studies indicate that EMBP is more concentrated in tumor cells than in brain and we have reported that tumor cells are more sensitive to estramustine than astrocytes. These data suggest that EMBP may confer a therapeutic advantage for agents which bind to this protein and form the basis for the development of new antimicrotubule agents for glioma therapy. (Supported by R-01 CA56764 to J.P.)

IN VIVO **RADIATION SENSITIVITY OF GLIOBLASTOMA MULTIFORME,** A. Taghian, W. Budach, J. Freeman, D. Gioioso, H. D. Suit, Edwin L. Steele Laboratory, Department of Radiation Oncology, Massachusetts General Hospital, Harvard Medical School, Boston, MA

Human glioblastoma (GBM) is one of the most resistant tumors to radiation. In two previous reports, we have studied 21 and analyzed 85 malignant glioma cell lines *in vitro*, respectively. We have demonstrated a wide range of sensitivity which is judged to be not compatible with the invariably fatal clinical outcome of these tumors. Namely, some of these cell lines were found to be relatively quite sensitive. However, in the *in vitro* conditions, the cells are cultured in the optimal nutritional and aerobic conditions. The TCD_{50} (the radiation dose necessary to control 50% of the tumors locally) determined in lab animals is analogous to the use of radiation with curative intent in clinical radiation oncology. The aim of the present study is to evaluate the sensitivity of GBM *in vivo* relative to that of squamous cell carcinoma (SCC) xenografts. The TCD_{50} assay was used to study 9 human tumor lines (5 GBM, 2 SCC, 1 STS, and 1 cancer colon). For further suppression of the residual immune system, all the animals received 6 Gy whole-body irradiation one day before transplantation. The mean tumor diameter at start of radiation was 6-7 mm. Local tumor irradiations were given in single dose, under conditions of clamp hypoxia (to avoid the influence of varying O_2 supply). For the purpose of the statistical analysis, a total of 8 TCD_{50} values were added (duBois et al, unpublished data). These experiments were performed by different investigators in the same laboratory using the same techniques under the same conditions. Five of them were GBM and three SCC xenografts. The TCD_{50} values for the 10 GBM xenografts varied between 32.5 and 75.2 Gy with an average of 46.8 $\pm$ 13.1 Gy. The TCD_{50} values for the SCC varied between 26.1 and 54.4 Gy with an average of 42.3 $\pm$ 10.1. The difference between the average TCD_{50} of GBM and SCC was not significant. The soft tissue sarcoma and cancer colon xenografts had a TCD_{50} of 46.0 and 49.2 Gy, respectively. No correlation was found between the TCD_{50} *in vivo* and the SF_2 or D_0 of the corresponding cell line *in vitro*. Our data on GBM xenografts show a wide range a sensitivity *in vivo* which does not correlate with the invariably fatal clinical outcome of these patients. Our *in vivo* and *in vitro* data on GBM (Taghian *et al* 1992, 1993) suggests that radiation sensitivity alone does not explain the cause of the poor clinical response of GBM to radiation, and that other factors could contribute to this response.

DETERMINANTS OF RADIOSENSITIVITY IN HUMAN MALIGNANT GLIOMA CELLS.

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We are investigating the determinants of radiosensitivity in human malignant glioma. Using radioresistant and radiosensitive glioma cell lines, we tested whether i) cells with aberrant p53 expression are more radiosensitive ii) apoptosis is a contributing factor in radiosensitivity and iii) radiosensitive cells were DNA double strand break (dsb) repair deficient. Expression of p53 was determined by Northern blot analysis and has been previously published (Oncogene 7:1879). Terminal deoxynucleotidyl transferase mediated biotinylated deoxyuridine nick end labeling was used to identify apoptotic cells. Electrophoresis was used to detect DNA fragmentation patterns. Pulsed field gel electrophoresis was used to study DNA dsb repair. Results indicated that i) there was no correlation between p53 expression and cellular radiosensitivity ii) the ability of cells to arrest in G1 following irradiation did not correlate with p53 mRNA expression iii) some relatively radiosensitive glioma cells lines display features characteristic of apoptotic cell death following radiation treatment and iv) failure to repair DNA dsb's was observed in only radiosensitive cell lines. These results suggest that differences in induction of apoptosis and DNA dsb repair contribute to variations in radiosensitivity of human malignant glioma. Supported by an award from the National Cancer Institute of Canada.

BRAIN GROWTH FAILURE FOLLOWING RADIATION THERAPY OF CHILDHOOD BRAIN TUMORS.

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Radiation therapy is an important adjunct in the management of many brain tumors. It has prolonged survival time for children and adults with certain types of brain tumor, but recently has been recognized to have adverse effects on intellectual and/or endocrine function. Growth hormone deficiency, with reduced linear growth, has been documented following irradiation of childhood brain tumors. In this report we describe 4 patients who received whole brain radiation therapy, at ages ranging from 8 months to 7 years, with long term survival but failure of brain growth post treatment. Each had normal brain and linear growth prior to treatment. Two children had growth hormone deficiency, but two have had normal linear growth. Tumor types included 1 recurrent frontal teratoma, 1 malignant astrocytoma, 1 medulloblastoma, and 1 presumed giant cell astrocytoma. The 4 patients are still alive, 11 to 15 years post treatment. All show impaired cognitive function. MRI imaging has been done, but has failed to show a specific cause for this unusual phenomenon. Clinical details of these 4 cases will be presented.

PERMANENT MYELOPATHY FOLLOWING RE-IRRADIATON OF THE SPINAL CORD:

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To assess the latent time and dose-fractionation factors associated with radiation myelopathy following retreatment to the spinal cord, a retrospective analysis was undertaken of all patients from the Princess Margaret Hospital registered between 1955 to 1985, and who developed permanent radiation myelopathy. There were 22 males and 13 females with ages ranging from 30 to 72 years. Twenty-four patients developed myelopathy after one course of radiation therapy and 11 following retreatment. Seven patients had histological confirmation of radiation myelopathy at autopsy. The actuarial survival was 14% at 5 years (median 8.3 months) from the day of diagnosis of radiation myelopathy. Latent times for myelopathy following a single course of treatment (mean 18.5 months, 7 - 57 months), were significantly longer than those after retreatment (mean 11.4 months, 4 - 25 months), p = 0.03. There was not a single incident of myelopathy in patients who received fractionated radiotherapy given once daily to an extrapolated response dose (ERD) of 100 Gy_2 or less (equivalent to 50 Gy in 25 daily fractions, $\alpha/\beta = 2$ Gy). Four patients who received an ERD less than 100 Gy_2 were all treated on accelerated fractionation protocols with multiple fractions given per day. Patients who were re-irradiated received significantly higher doses (mean ERD 148 Gy_2) than those who had a single course of treatment (mean ERD 121 Gy_2).We conclude that the risk of radiation myelopathy following conventional fractionation to the spinal cord is extremely small; giving multiple fractions per day reduces the spinal cord tolerance; latent time to myelopathy decreases following retreatment; and there is possible long term recovery of radiation damage in human spinal cord.

ASSOCIATION OF CELL PROLIFERATION (%S, $\%G_2M$) AND HISTOLOGIC GRADE WITH SURVIVAL IN OLIGODENDROGLIOMAS

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Background/Materials/Methods: The tumors of 82 previously reported patients with supratentorial oligodendroglioma treated at the Mayo Clinic between 1960-82 (Shaw et al, J Neurosurg 76:428-434, 1992) were subject to flow cytometric assessment of ploidy (n=70) and cell proliferation (n=57). Tumor grade (St. Anne-Mayo method) was as follows: 4% grade 1, 23% grade 2, 51% grade 3, and 21% grade 4. Thirty-nine percent of tumors were diploid and 61% aneuploid. For %S-phase determination the low, middle, and high tertile values were <6%, 6 to <9%, and $\geq$9%; the corresponding values for $\%G_2M$ were $\leq$5%, >5 to 12%, and >12%.

Results: Low tumor grade (p=0.08), low %S tertile (p=0.02), and low $\%G_2M$ tertile (p=0.01) were found to be univariately associated with increased survival. There was no evidence that survival differed with respect to ploidy (p=0.85).

%S Tertile	n	Survival Median (yr)	Survival 5-yr (%)	Std Error(%)	%G2M Tertile	n	Survival Median (yr)	Survival 5-yr (%)	Std Error(%)
Low	22	9.5	73	9	Low	21	10.0	67	10
Mid-High	35	3.9	39	8	Mid-High	36	3.5	44	8

Tumor grade (low=1+2 and high=3+4) and cell proliferation (%S + $\%G_2M$) were combined to produce four prognostic groups (p=0.03):

Group	Group: Grade		Group: %S+G2M Tertile	n	Survival Median (yr)	Survival 5-yr (%)	Std Error(%)
1	Low	+	Low	5	NR	80	18
2	Low	+	Mid-High	10	7.5	70	14
3	High	+	Low	13	7.5	69	13
4	High	+	Mid-High	29	3.0	33	9

Conclusions: Tumor grade and cell proliferation, as well as the combination of both factors, are significant predictors of survival in oligodendrogliomas whereas ploidy is not.

In Vivo Biochemical Effects of Tamoxifen on Malignant Gliomas Studied with 1H MR Spectroscopic Imaging (MRSI). M. Preul, G. Shenouda, A. Langleben, JG. Villemure, D. Arnold, Montreal Neurological Institute, McGill University, Montreal, Canada

Tamoxifen (TMX), a protein kinase C inhibitor, has been approved to treat patients with recurrent malignant gliomas. To elucidate the in vivo biochemical effects of TMX, we serially measured changes in resonances from choline-containing phospholipids (Cho), phosphocreatine + creatine (Cr), N-acetylaspartate (NAA), lactate (LA), and lipid (Lip) in 13 patients with tumors using MRSI (state-of-the-art chemical shift imaging yielding 1H spectra from multiple 1 cc tissue volumes). Patients underwent serial MRSI before and during TMX from 2 weeks to 12 months. Six patients responding to TMX had decreases in LA (45%) and Lip (100%), $p<0.001$ each, by 1 month, and in Cho (23%), $p<0.05$, by 6 months. LA, Lip, Cho remained decreased in all responders. Seven patients failing TMX showed no decreases in LA, Lip, or Cho by 1 month ($p<0.0001$); 2/7 showed increased LA and Lip ($p<0.001$). Chemical changes in spectral peaks and PET-like MRSI metabolite images preceded and correlated with changes in clinical status and on infused CT and MRI for responding or failing patients. Serial MRSI reveal early biochemical changes in malignant gliomas treated with TMX: 1) responders show marked decreases in LA and Lip by 1 month; 2) decreases in LA, Lip, and Cho suggest decreased tumor anaerobic glycolysis and cell destruction; 3) tumor progression and failure of TMX correlates with failure of metabolites to change by 1 month. MRSI, which allows regional, retrospective, in vivo study of tumor biochemistry, is a convenient, powerful, noninvasive tool to monitor and quantify TMX therapy of brian tumors, and predict treatment response or failure.

A PHASE I/II TRIAL OF HIGH DOSE TAMOXIFEN IN PATIENTS WITH RECURRENT HIGH GRADE CEREBRAL ASTROCYTOMAS. G. Shenouda, M. Preul, A. Langleben, JG. Villemure, JP. Bahary, I. Wainer, M. Pollak, B. Leyland-Jones, A. Tsatoumas, A. Choi. McGill University, Montreal, Quebec, CANADA.

Thirty patients were accrued on study, 15 males and 15 females, with a median age of 46 y. (24-67). Fourteen patients had grade III, and 16 grade IV recurrent astrocytomas with a median Karnofsky P.S. of 70 (50-100). Tamoxifen (TMF) was given at a dose of 120 mg/m^2 BID PO for 8 weeks at which time a CT scan was done and compared to pre-treatment CT for assessment of response. Magnetic Resonance Spectroscopy Imaging (MRSI) was used to evalute the Tamoxifen-induced in vivo biochemical changes in lactate (La) and lipid (Lip) content of tumors. Survival distributions were assessed using the Kaplan-Meier method. With a median length of follow-up of 16 weeks, the overall survival was 24 weeks. Five patients had a partial response (PR) with $\geq$ 50% reduction of tumor volume on CT scan as compared to pre-treatment measurements. The median duration of PR was 33 weeks (6-47). Two additional patients had clinical and radiological stable disease (SD) for a duration of 25, and 26 weeks. MRSI demonstrated significant reduction of La and Lip levels of 45% and 100%, respectively in patients with PR and SD as compared to patients with disease progression ($p=0.001$) within one month of starting TMF. Toxicity consisted of 3 grade I/II, and 5 grade III/IV nausea and vomiting. Serum N-Desmethyl TMF/TMF ratios were significantly higher in patients with nausea and vomiting 2.37±0.44 than in patients without this side effect 1.74±0.27 ($p=0.0007$). Serum IGF-1 levels were decreased in all patients from a pretreatment level of 1.14±0.5 U/ml to 0.83± U/ml. Results are suggestive of a potential role of TMF in the management of patients with recurrent high grade astrocytomas with acceptable tolerance. In addition, this is the first report of monitoring the in vivo biochemical TMF-induced changes in this group of patient by MRSI.

LOH ANALYSIS OF GLIOMAS IN FAMILIES. C.Watling, D.van Meyel, D.Ramsay, G.Cairncross, Depts of Clinical Neurological Sciences, Oncology and Pathology, University of Western Ontario and London Regional Cancer Centre, London, Canada

Background: Studies of sporadic malignant gliomas have identified structural abnormalities in a number of chromosomal regions including losses of DNA on 9p, 10 and 17p. **Purpose:** We undertook the following molecular analysis in families with glioma (Can J Neurol Sci 19:492-7,1992) to determine whether chromosomal losses on 9p, 10 and 17p were more frequent in *inherited* than sporadic tumors. **Methods:** Genomic DNA was extracted from tumor tissue and peritumoral normal tissue or blood from 20 patients with a family history of glioma. Dinucleotide repeat polymorphisms (microsatellites) were analyzed by polymerase chain reaction (PCR) to assess loss of constitutional heterozygosity (LOH) on 9p, 10 and 17p. Three polymorphic markers on chromosome 9 (D9S104, D9S161, D9S165), one on chromosome 10 (D10S209), and two on 17p (D17S786, D17S796) were used. Autoradiographic films were analyzed for LOH after radioactively labelled PCR products were resolved on denaturing formamide-acrylamide gels. **Results:** Of 20 patients informative for at least one of three chromosome 9 markers, 12 (60%) showed LOH at one or more loci; of 9 informative for the chromosome 10 marker, 4 (44%) showed LOH; and of 16 informative for at least one of two chromsome 17 markers, 7 (44%) showed LOH at one or both loci. **Conclusions:** Microsatellite markers can be used to detect LOH in archival glioma tissue. As in sporadic gliomas, frequent LOH was observed on 9p (9p22), 10 and 17p. Further work will be required to determine whether the proportion of LOH in these chromosomal regions is higher in *familial* gliomas than sporadic ones, as might occur with an inherited suppressor gene conferring susceptibility to gliomas in families.

GLIOBLASTOMA MIGRATION CAN BE BLOCKED BY NON-TOXIC INHIBITORS OF INTEGRIN AND MYOSIN FUNCTION. S.S. Rosenfeld, G.Y. Gillespie, and C.L. Gladson, University of Alabama at Birmingham, Birmingham, AL 35294

Glioblastoma multiforme (GBM) can invade normal brain, and this presents an enormous challenge to the management of patients with this malignancy. Invasiveness requires: 1) integrin-mediated attachment to arginine-glycine-aspartate (RGD) sequences in the extracellular matrix (ECM) and 2) cell motility, which is driven by the cytoplasmic molecular motor myosin. We have utilized an *in vitro* invasion assay to examine effects of specific inhibitors of integrin and myosin function on GBM invasiveness. U251MG cells, which express two integrins specific for the ECM protein vitronectin, were plated in a modified Boyden chamber migration assay, utilizing 8 micron pore polycarbonate filters. We have previously established that over 50% of U251MG cells migrate in this assay *specifically* toward vitronectin in a dose and time-dependent manner, mediated by two integrins (C.L. Gladson, *et al.*, submitted). We found that migration could be blocked by 90% with 700 nM echistatin, a peptide derived from the venom of the pit viper *Echis carinatus*, which specifically blocks integrin binding to RGD sequences. Echistatin had no effect on 3HTdR uptake over this concentration range. Cytoplasmic myosin is inactive unless phosphorylated by myosin light chain kinase (MLCK). The MLCK inhibitors ML7 and KT5926 blocked U251MG migration by >95%, at concentrations that did not alter 3HTdR uptake but which have been reported to abolish myosin phosphorylation. The values of Ki for ML7 and KT5926 were approximately 5000 and 500 nM, respectively. No inhibition of migration was seen with inhibitors of cAMP or cGMP-dependent protein kinases over a comparable concentration range. We conclude that inhibitors of RGD-dependent integrin function and myosin activity can selectively block invasion of a GBM cell line at non-toxic concentrations, and these agents thus represent a new approach to modulating the malignant behavior of this tumor.

ISG WAND-DIRECTED RESECTION OF LOW GRADE ASTROCYTOMAS IN CHILDREN: Experience with 30 cases treated at the Hospital for Sick Children. J.T. Rutka, JM Drake, HJ Hoffman, RP Humphreys, and S. Holowka. Hospital for Sick Children, University of Toronto

Low grade astrocytomas are the commonest intracranial neoplasms in children. Surgery remains the treatment of choice for children with symptomatic low grade astrocytomas. However low grade astrocytomas in midline axial or eloquent locations of the brain have been approached with caution in the past because of the untoward morbidity associated with resecting tumors in these regions. In an attempt to maximize the surgical resection of deep seated intracranial tumors, we have utilized the ISG-viewing wand as a surgical adjunct in 30 children with low grade astrocytomas over the past 2 years. The viewing wand is a six-jointed, six degree of freedom mechanical articulated arm for 3-dimensional localization linked to a computer graphics workstation for dynamic image display. Nine children had tumors in the thalamus, 4 in the hypothalamus, 3 in the midbrain, 5 in the posterior fossa, 4 in the parietal region, 3 in the occipital region, and 2 in the optic chiasmatic region. Post-operative scans have demonstrated a total resection in 12 patients (40%), subtotal (>80%) in 10 patients (33%), and a 50% resection in 8 patients (27%). Only 2 patients have received radiation therapy in the post-operative period. While difficult to prove the efficacy of image-directed surgery, it is our impression that the intraoperative use of the ISG-wand for low grade astrocytomas in children aids the surgeon in bone flap placement, planning the most direct trajectory towards the tumor, and facilitating a more complete surgical resection of the tumor with less morbidity than could be achieved without the device. As experience continues with the ISG wand, we will determine if a more radical resection of low grade astrocytomas is accompanied by longer disease free survivals for children.

TRANSFACIAL EXPOSURE FOR TREATMENT OF TUMORS OF THE ANTERIOR SKULL BASE AND CLIVUS
Mark G Hamilton (Foothills Hospital, Calgary), S. Beals, E. Joganic, and R. Spetzler (Barrow Neurological Institute, Phoenix)

Resection of extensive, deep seated neoplasms involving the anterior skull base and clivus remains a surgical challenge. The anatomic site of these lesions can be used as a guide to classify a logical approach for transfacial exposure. We have defined six levels at which facial osteotomies can be performed to provide excellent exposure for tumor resection. These include exposures by a transfrontal (Level I), transnasal (Level I), transfrontal nasal-orbital (Level III), transnasomaxillary (Level IV), transmaxillary (Level V), or transpalatal (Level VI) route. These approaches provide direct access to lesions of the anterior skull base and clivus, thereby minimizing brain retraction. All of these approaches, with the exception of Level IV, can be accomplished without the need for a facial incision.

We present our experience with 15 patients who underwent transfacial exposure for resection of extensive anterior skull base or clival neoplasms. Tumor histology included: 5 chordomas; 3 juvenile angiofibromas; and one each of melanoma, chondrosarcoma, fibrosarcoma, malignant fibrous histiocytoma, V_2 plexiform neurofibroma, encephalocele, and pituitary adenoma. Surgical exposures utilized for treatment of these 15 patients included 19 levels: 1 each of Level I and Level II; 5 Level III; 2 Level IV; 9 Level V; and 1 Level VI. Four patients had multiple levels utilized (Level III and Level V). There was no significant surgical morbidity and no surgical mortality. Eleven of the 15 patients survive. Four patients have died, all as a consequence of tumor progression. We conclude that the transfacial approaches have an important role in the treatment of deep seated lesions of the anterior skull base and clivus.

CONTINUOUS LOW-DOSE ORAL VP-16 FOR PATIENTS WITH RECURRENT MALIGNANT GLIOMA Fulton DS, Urtasun RC, Cross Cancer Institute, Edmonton, Alberta Canada

VP-16 is effective for treatment of patients with malignant glioma when given intravenously in high doses. However, because the percentage of dividing cells in malignant glioma may be small, cell cycle specific drugs, such as VP-16 may be more effective if given continuously over a prolonged period. When prolonged oral VP-16 is given at a dose of 50 mg/m^2/day, temporary interruptions of therapy are required because of myelosuppresion. In this study, the dose of 50 mg/day was chosen in the hope that interruptions of therapy would not be required. VP-16, 50 mg/day was given orally until the neutrophil count dropped to <1.0 or the platelets fell to <75,000 and resumed when the counts rose to normal levels. Thirty-seven patients with malignant glioma (13 aa, 17 gbm, 7 anaplastic oligo) were treated at the time of tumor progression. All had KPS≥70 at study entry. All patients had prior RT, 10 with adjuvant nitrosourea. 22 had prior nitrosourea chemotherapy for tumor recurrence, 5 had no prior chemotherapy. 16 patients were treated with VP-16 at first recurrence, 21 at 2nd or 3rd recurrence. All patients had CT or MR scans and clinical evaluation every 8 weeks. Median TTP was 9.0 weeks for all patients, 9.1 wk for those treated at first progression and 9.1 wk for those treated at 2nd or 3rd progression, 10.0 wk for aa and 6.8 wk for gbm. Median survival was 23.6 wk for all patients, 18.5 for those treated at first recurrence and 26.0 wk for those treated at 2nd or 3rd progression, 38.4 wk for aa and 14.2 wk for gbm. There were 6 partial responses and 8 patients with stable disease for at least 8 weeks (R+SD=41%). The study suggests that prolonged low-dose oral VP-16 is effective for patients with malignant glioma previously treated with nitrosourea and is more effective for aa than gbm.

MOP (MECHLORETHAMINE, VINCRISTINE, PROCARBAZINE) IN RECURRENT GLIOMA: A SECOND OPINION. J. C. Buckner[1], P. L. Schaefer[2], R. P. Dinapoli[1], J. R. O'Fallon[1], P. A. Burch[1]. North Central Cancer Treatment Group; [1]Rochester, MN; [2]Toledo, OH

Previous investigators reported objective tumor regression in 52% of 27 patients (pts) with glioma recurrent following radiotherapy. (J Clin Oncol 8:2014-2018, 1990). In order to confirm those promising results, we repeated the methodology of the previous clinical trial and report the following preliminary results. All 47 pts had histologic proof of glioma, CT or MRI evidence of tumor recurrence after radiation, and Zubrod performance score 0-2. Median age was 51 years (range 21-71). 32 pts with and 15 pts without prior nitrosourea received mechlorethamine 3 or 6 mg/m^2 IV, respectively, days 1 and 8, vincristine 2 mg IV days 1 and 8, and procarbazine 100 mg/m^2/d p.o. days 1-14, with cycles repeated every 28 days. To date, only 7 pts (15%) have demonstrated objective tumor regression; all had prior nitrosourea. 6 pts (13%) have been stable ≥6 months. Duration of regression ranged from 6.6 to 20.1+ months with 5/7 pts with regression alive without tumor progression at 7.8 to 20.1 months. Regressions by tumor grade include: grade 1:0/1; 2:2/10; 3:4/14; 4:1/21; unknown: 0/1p. Toxicity consisted primarily of myelosuppression. The median leukocyte nadir was 1800/mcL; the median platelet nadir was 100,000/mcL. 8/45 pts developed leukopenia < 1000/mcL and there were 2 deaths related to infection during neutropenia. 4/45 pts developed thrombocytopenia < 20,000/mcL without bleeding episodes. There was a trend toward cumulative myelosuppression with repeated cycles of chemotherapy. Nonhematologic toxicity consisted of vomiting in 34% and vincristine-related neurosensory toxicity in 13%. In conclusion, we could not confirm the high regression rate reported previously by others. Most regressions occurred in pts with grade 2 or 3 gliomas and these responses were durable. MOP is reasonable salvage therapy in such pts. The regimen is inactive in patients with grade 4 glioma. Myelosuppression is substantial, including the risk of fatal infection.

REPEATED INTRATHECAL TREATMENT OF RELAPSED PNET WITH RADIOLABELLED MONOCLONAL ANTIBODIES. CL Chandler, K Hopkins, HB Coakham, J Bullimore, JT Kemshead, Imperial Cancer Research Fund, Frenchay Hospital, Bristol Oncology Centre, Bristol, U.K.

Primitive neuro-ectodermal tumours(PNET) are one of the commonest childhood tumours and share a tendency to spread along the CSF pathways. Since 1986 we have been involved in Phase 1/2 trials investigating the treatment of relapsed PNET with targetted intrathecal radiotherapy, using monoclonal antibodies conjugated with radioactive iodine. Treatment is administered via an Ommaya reservoir, and regular blood, CSF and urine samples taken to allow us to calculate dosimetry and pharmacokinetics. We have treated 22 patients (age range 6-62) with doses ranging from 555-4700 MBq. 6 patients have undergone repeated injections with escalating doses of radiation. Whole body clearance of I-131 occurred more rapidly with subsequent injections due to the presence of human anti mouse antibodies(HAMA). Blood clearance following the 2nd and 3rd injections was much faster in comparison with CSF clearance which did not significantly change. This resulted in a comparative fall in the dose received by the bone marrow compared with that received by the tumour tissue which was actually increased. Toxicity has been minimal. 45% of patients have developed a self limiting chemical meningitis, one patient went into staus epilepticus, and all patients have developed some degree of reversible bone marrow suppression, which was reduced in patients undergoing repeated injections. Complete remissions were obtained in 4 patients (mean survival following intrathecal treatment 45 months), partial responses in 1 (48 mnths), in 5 patients the disease remained static (11.6 mnths), and there was no response in 7 (2.8 mnths). Dosimetry and pharmacokinetic data have shown minimal doses of radiation to unaffected brain and bone marrow, and the role of HAMA will be discussed. Targetted radiotherapy may represent a significant advantage over other forms of treatment of leptomeningeal relapse of PNET.

STEROID-INDUCED MR SCAN CHANGES IN PATIENTS WITH RECURRENT MALIGNANT GLIOMA. C.Watling, D.Lee, D.Macdonald, G. Cairncross, Departments of Clinical Neurological Sciences, Radiology and Oncology, University of Western Ontario, and London Regional Cancer Centre, London, Canada.

Purpose: We evaluated the magnitude and time course of steroid-induced MR scan changes in patients with recurrent malignant glioma concerned that steroid therapy concurrent with investigational treatment might result in false-positive responses. **Methods:** Ten symptomatic patients not on steroids when their malignant glioma recurred had a pre-steroid baseline MR scan followed by serial scans at weekly intervals for one month while on dexamethasone (16 mg/day). The maximum cross-sectional areas and volumes of the total abnormal regions and the gadolinium-enhancing regions were compared quantitatively and qualitatively for each series of scans. **Results:** Nine of ten patients (90%) had a measurable reduction in the size of the total abnormal region or enhancing region with steroid treatment. Maximum measurable improvement was evident within two weeks in most. The maximum cross-sectional area and volume of the total abnormal region decreased by at least 25% in five of ten patients (50%). The maximum cross-sectional area and volume of the enhancing region decreased by at least 25% in three of ten (30%). Scans were judged improved by the reporting neuroradiologist in seven of ten (70%). Subjective improvements were also evident within two weeks but described as slight or modest. **Conclusions:** Steroid-induced MR scan reductions in the size of malignant gliomas may confound the assessment of response to investigational agents. For patients starting steroids for symptom control, we suggest that investigational treatment be delayed until a new baseline MR image is established two weeks later. Response is then judged by comparing subsequent scans to the new steroid-influenced baseline MR scan.

IS BRACHYTHERAPY WORTHWHILE FOR PATIENTS WITH RECURRENT MALIGNANT ASTROCYTOMA? Mark Bernstein, Normand Laperriere, Stephen McKenzie, Jennifer Glen, University of Toronto, Toronto, Canada

We report our experience with 46 patients with recurrent malignant astrocytoma treated with stereotactic high-activity iodine-125 brachytherapy between October 1986 and October 1992. The patients had been initially treated for glioblastoma (32), malignant astrocytoma (12), or low-grade astrocytoma (2) with surgery and external fractionated radiation. The median interval from initial diagnosis to time of recurrence treated with brachytherapy was 54 weeks. Twenty-five patients (54.3%) were treated with chemotherapy prior to brachytherapy. All patients received a minimum brachytherapy dose of 70 Gy at a median dose rate of 68 cGy/hr. All but three patients have died as of January 1994; the median survival time for all patients is 46 weeks post-implant (product limit estimate method). The three surviving patients are alive 80, 85, and 210 weeks post-implant. Karnofsky score ≥ 80 and age ≤ 45 years at the time of implant were significantly correlated with survival time following brachytherapy. Twelve patients (26.1%) underwent re-operation for radiation necrosis at a median interval of 28 weeks post-implant. Five patients (10.9%) incurred complications from brachytherapy. Forty-four patients are evaluable regarding pattern of failure following brachytherapy; 6 (13.6%) recurred at a distance from the treatment volume (four in brain and two in spinal subarachnoid space). We conclude that brachytherapy is of benefit in selected patients with recurrent malignant astrocytoma and superior to simple resection and/or chemotherapy alone. However complications are significant, re-operation frequently required, and failure outside the treatment volume common. Furthermore, only about 10% of all patients with recurrent malignant astrocytoma are eligible for brachytherapy based on clinical and imaging criteria.

LARGE EFFECT OF AGE ON SURVIVAL OF PATIENTS WITH GLIOBLASTOMA TREATED WITH RADIOTHERAPY AND IMPLANT BOOST. PK Sneed, PG Gutin, DA Larson, MW McDermott, MD Prados, WM Wara, KA Weaver; University of California, San Francisco, CA 94143 USA

From January 1981 through December 1992, 160 adults (≥17 years old) with primary glioblastoma multiforme underwent high-activity iodine-125 brain implant boost without hyperthermia after external beam radiotherapy. Age is a well-known prognostic indicator, but this large experience permitted an analysis of survival by patient decade, graphically illustrating this point and showing surprisingly good survival for patients <30 years of age.

There were 99 males and 61 females ranging in age from 17.5-73.2 years. KPS ranged from 70-100 (median 90). Surgery prior to radiotherapy consisted of biopsy in 12 patients, subtotal resection in 106, and gross total resection in 42. External beam radiotherapy dose ranged from 40.0-76.8 Gy, with 143 patients receiving 59.4-61.0 Gy. The prescribed brachytherapy dose ranged from 35.7-79.2 Gy (median 55.1 Gy) at 30-70 cGy/hr (median 41.5 cGy/hr) using 1-16 sources (median 6) in 1-6 catheters (median 3). Reoperations were performed in 79 patients (49.4%).

The 9 patients <30 years old had a 3-year survival rate of 77.8% and median survival has not yet been reached, with follow-up of 89.4-510.9 weeks (median 192 weeks). The 18 patients ≥30 and <40 years old had a median survival of 138.7 weeks, compared with 105.3 weeks for 46 patients ≥40 and <50, 77.1 weeks for 48 patients ≥50 and <60, and 69.9 weeks for 39 patients ≥60. The effect of other parameters on survival will also be presented.

Age group	<30	30-40	40-50	50-60	>60
Median surv. (wk)	N.R.	138.7	105.3	77.1	69.9

PERMANENT IODINE-125 INTERSTITIAL IMPLANTS FOR THE PRIMARY TREATMENT OF MALIGNANT GLIOMAS.
L. Gaspar[1], L. Zamorano[1], L. Garcia[1], F. Shamsa[1], C. Warmelink[1], D. Yakar[2], [1]Wayne State University, Detroit, Michigan, [2]Henry Ford Hospital, Detroit, Michigan

Local tumor persistence or recurrence is the most common pattern of relapse following treatment of malignant gliomas with conventional external beam radiation, with or without chemotherapy. In an effort to reduce local recurrence without an unacceptably high incidence of radiation necrosis, permanent iodine-125 interstitial implants have been performed in 72 patients with newly diagnosed malignant gliomas. Patients ranged in age from 12 to 79 years, median of 44 years. The tumor was an anaplastic astrocytoma or glioblastoma multiforme in 45 and 27, respectively. External beam radiation (50-60 Gy) was done before the implant in 44 patients, after the implant in 17. Ten patients did not undergo additional external beam radiation. The implant was planned using stereotactic technique to encompass the postoperative enhancing tumor identified on computerized tomography with the 5 cGy per hour isodose curve (10.368 Gy at infinity). Acute complications post-implant were uncommon. Late complications included radiation necrosis in 14 patients (19%), brain abscess in 2 (3%), and scalp necrosis in 1 (1%). Forty-eight patients (67%) are still alive. Updated Kaplan Meier survival curves will be presented but preliminary statistics demonstrate a one year survival of 85% and 80% for glioblastoma and anaplastic astrocytoma, respectively. Permanent iodine-125 implants in newly-diagnosed maligant glioma are well tolerated. Survival statistics are encouraging.

CURRENT RADIOSURGERY PRACTICE: RESULTS OF AN ISRS SURVEY.
DA Larson[1], C Lindquist[2], JS Loeffler[3], LD Lunsford[4]. [1]University of California San Francisco, [2]Karolinska Institute, [3]Brigham and Women's Hospital, [4]University of Pittsburgh.

We distributed a questionnaire in November, 1993 to the entire membership (N=171) of the International Stereotactic Radiosurgery Society to obtain information on current radiosurgery practice patterns. Responses were obtained from 15 Gamma Knife and 32 linac radiosurgery facilities located in 9 countries and representing 115 members (67% response rate). Respondents reported 5671 Gamma Knife procedures and 5724 linac procedures carried out during 1982-1993.

Results reflecting current radiosurgery practice patterns will be presented, including: (1) indications for radiosurgery, (2) types of specialists who perform radiosurgery, (3) number of specialist hours required per patient on day of treatment; and (4) relative distribution of follow-up responsibility. Statistically significant practice differences will be presented, based on type of equipment used and level of experience (number of patients treated), and results will be compared to those obtained in a recent ASTRO survey. In North America most radiosurgery procedures are labor-intensive, and are carried out with a multidisciplinary team of specialists from neurosurgery, radiotherapy, radiology, medical physics, and nursing.

STEREOTACTIC FRACTIONATED RADIOTHERAPY IN MENINGIOMAS : RESPONSE AND COMPLICATIONS.
JG Villemure, JA Espinosa, L Souhami, JP Bahary, JL Caron, A Olivier, EB Podgorsak. McGill University, Montreal.

Sixteen patients with meningiomas progressing after subtotal resection or estimated not to be surgical candidates were treated with fractionated stereotactic radiotherapy;these are reviewed from the point of view of response and complications. All received a total dose of 42Gy prescribed at the 90% isodose surface corresponding to the periphery of the tumor on contrast MRI or CT. The treatments were administered in 6 fractions, on alternate days over 2 weeks.

At median follow-up of 27 months (20 to 52), 14 of the 16 tumors have shown no progression in volume, with half this group demonstrating either reduction in volume or central necrosis. Two tumors continued to grow.
Four patients presented delayed neurological complications manifested by neurological deficits not related to tumor progression but rather to brain oedema or radionecrosis involving brain adjacent to tumor. These complications were seen in tumors where 3 cm and 4 cm cones were used.

Radiosurgery or fractionated stereotactic radiotherapy for the treatment of some meningiomas appear effective in controlling tumor progression. Complications appear to correlate with radiation cone size. We recommend caution in using single cone greater than 2.5 cm in diameter with the current total dose for treatment of meningiomas.

Correlation Between Flow Cytometric and Molecular Biological Methods for Detection of Mutant p53 in Cultured Glioma Cells.
H.B. Newton, M.D. Kotur, A.C. Papp, T.W. Prior. The Ohio State University Hospitals, Columbus, Ohio, USA.

p53 is a transcription factor involved in cell cycle control that acts as a tumor suppressor gene and is implicated in the transformation of gliomas. We compared the ability of flow cytometry (FCM) and molecular methods to detect mutant p53 ($p53_m$) in glioma cultures. Nine glioma cell lines (8 astrocytic [1 pilocystic, 2 anaplastic, 5 glioblastoma] and 1 medulloblastoma) and controls were analyzed by FCM using indirect immunofluorescence techniques. Eight cell lines were $p53_m$ positive, while one cell line (anaplastic) was $p53_m$ negative, compared to controls. DNA from each cell line and controls was then amplified in a triplex polymerase chain reaction (PCR) spanning p53 exons 2-4, 5-6, and 7-9. The PCR product was screened for mutation using multiplex heteroduplex analysis (HA). Identical heteroduplex bands were found in exon 5 in seven of 9 cell lines. DNA sequencing identified a cytosine to adenine transversion, causing substitution of proline for histidine, within codon 179 of all 7 cell lines. Additional heteroduplex bands were found in exon 3 in one cell line and exon 8 in another. The concordance rate for detecting $p53_m$ between FCM and HA was 78% (7 of 9). This study suggests that FCM and HA are accurate, complementary, techniques for screening glioma cells for $p53_m$.
Supported by NINDS (USA).

MOLECULAR AND MRI QUANTITATION OF AN INTRACRANIAL GLIOMA MODEL. T. Mikkelsen, N. Roosen R. Chopra, J. Windham, M.L. Rosenblum. (Depts. of Neurology, Neurosurgergy & Radiation Physics, Henry Ford Hospital, Detroit, MI).

We have established an intracerebral nude rat xenograft model of human malignant glioma, which illustrates the temporal growth and invasion patterns histologically representative of those seen clinically. We use the established non-invasive methods of magnetic resonance imaging (MRI) to correlate histologic images registered with MR images in 3-dimensional space. We have stereotactically implanted the U251MGn glioblastoma cell line into either the caudate/putamen or corpus callosum of nu/nu rats. These animals are imaged using a 7T MRI system and sacrificed weekly over the 6 - 8 week lifespan of the implanted animal. A 100% incidence of tumor is obtained, detectable by MRI by 1 week. Molecular detection of single human tumor cells is achieved by detecting Alu repeats by Blur-2 in situ hybridization and image registration with MRI is performed for correlation. Image processing allows tumor segmentation and volume calculation of tumor and the infiltrative partial volume zones. Serial imaging validated by this histologic correlation will allow the quantitation of tumor growth and invasion following genetic manipulation of tumor cells or gene therapy or pharmacotherapy studies. The relevance of such studies to clinical work is significant, given the direct translation of this data to clinical MRI.

REDUCTION IN C6 TUMOR GROWTH THROUGH THE ADMINISTRATION OF COUMADIN. I.S. Vaithilingam Ph.D., W. McDonald BSc. and R.F. Del Maestro M.D., Brain Research Laboratories, Victoria Hospital, London, Ont., Canada.

Background: C6 astrocytoma cells release proteolytic enzymes required for the breakdown of the vascular basement membrane. Due to the heterogeneous composition of the basement membrane, a variety of proteolytic activities are required for dissolution of this structure. C6 astrocytoma cells release a high molecular weight protease or proteasome, which may be critical in the comprehensive breakdown of the basement membrane.
Methods: Purified extracellular proteasome was assayed separately on ^{3}H-collagen I and IV, ^{3}H α-casein and ^{3}H rat albumin. Coumadin was given I.P. at 0.25 mg/kg body weight on days 9, 11 and 13 of tumor growth. Oral adminstration of coumadin at 3.0 mg/l of drinking water was given after day 7.
Results: The extracellular proteasome (EP) degraded collagen I and IV, α-casein, rat albumin and ß-insulin. Proteolysis of these substrates was inhibited by different classes of protease inhibitors. Collagenase I activity was inhibited by the aspartic protease inhibitor, pepstatin. Collagenase IV activity was inhibited by the serine protease inhibitor, coumadin. Degradation of the remaining substrates was inhibited by the metalloprotease inhibitors, TIMP-1, TIMP-2 or EDTA. Rats implanted with C6 spheroids were treated with coumadin. Both p.o. and I.P. adminstration of coumadin resulted in reduction of tumor weight by 74% and 64% respectively.
Conclusions: It appears that a serine collagenase IV activity of an extracellular proteasome may be critical in the initiation of tumor induced angiogenesis. Complete inhibition of tumor growth may also require the administration of aspartic and metalloprotease inhibitors.

RELATIONSHIP OF HYPOXIA TO NECROSIS AND CELL CYCLE PROGRESSION IN A GLIOMA XENOGRAFT MODEL. Matthew Parliament, Allan Franko, Joan Turner and Bruce Mielke, Radiation Oncology and Radiobiology, Cross Cancer Institute, and Department of Pathology, University of Alberta Hospitals, Edmonton, Alberta, Canada.

Malignant gliomas frequently are observed to contain extensive necrotic regions, probably resulting from critical nutrient depletion, in particular for oxygen and/or glucose. Heterogeneity of oxygen tension may modify cellular radiosensitivity, cell cycle distribution and DNA synthesis as well. Glioma cell lines M059K and M006 have been characterized and passaged *in vitro*. These cell lines reproducibly form tumors in SCID mice. Our results show that these lines adapt readily to growth in hypoxic (0.66% O_2) conditions, with a colony forming ability identical to that of control cells grown under 18% O_2. The oxygen consumption rate of fresh tumor explants was approximately 20% of that of the same cell line grown *in vitro*, consistent with a markedly reduced respiratory rate *in vivo* in response to hypoxia. Also, low O_2 tension may modify cell cycle progression as the G1/S ratio is increased relative to controls. 3H-Misonidazole binds to tumor explants *in vitro* under hypoxic conditions, in a manner more consistent with murine tumors than other human cell lines tested to date. At tumor sizes between 200 and 800 mm^3, not all tumors contain necrosis; in those tumors which do contain necrosis, preliminary results indicate that hypoxic cells are sometimes, but not always identified at the periphery of necrotic regions. Supported by a grant from the Alberta Cancer Board.

Diagnosis of Intracranial Tumors using *In Vivo* Biochemical Spectral Pattern Recognition and 1H MR Spectroscopic Imaging (MRSI). M. Preul, JG. Villemure, W. Feindel, D. Arnold, Montreal Neurological Institute, McGill University, Montreal, Canada

We used MRSI (state-of-the-art chemical shift imaging yielding 1H spectra from multiple 1 cc tissue volumes) to evaluate biochemical characteristics of the 5 major brain tumors types in vivo and compared this with tumor histology. Resonances from choline-containing phospholipids, phosphocreatine + creatine, N-acetylaspartate, alanine, lactate, and lipids were measured in 60 untreated (except for steroids) patients with histology-proven brain tumors (glioblastoma = 14, astrocytoma II = 14, astrocytoma I = 11, metastasis = 14, meningioma = 7) before craniotomy or biopsy. Reinertz grading was used for astrocytomas. A large region of interest included the tumor and contralateral or remote MRI-normal-appearing brain. Control values came from homologous contralateral or remote voxels and 10 normal subjects. Multivariate analysis and computer-based spectral pattern recognition techniques were used to automatically classify the tumor spectra in multi-dimensional feature space. All 60 tumors and 10 normals from the training set were correctly classified on retesting compared to the 26% error rate for the primary diagnosis for the same group of tumors using CT, MRI, ± angiography. "Typical" biochemical profiles of 5 major types of brain tumors were identified for these 60 tumors. Combining MRSI with computer-based pattern recognition schemes, these data suggest that certain tumors can be assigned to diagnostic categories with known degrees of certainty based on their in vivo biochemical nature. MRSI offers thorough, regional, noninvasive biochemical and functional assessment of intracranial tumors and may reduce the need for surgical biopsy, thereby decreasing patient morbidity.

EFFECTIVE COMBINATION THERAPY FOR RADIOTHERAPY RESISTANT HIGH GRADE ASTROCYTOMA. Langleben, A., Preul, M., Tampieri, D., Tsatoumas, A., Bahary, J.-P., Shenouda, G., Baltuch, G., and Villemure, J.-G. McGill University, Department of Oncology, Montreal, Canada.

Patients with anaplastic astrocytoma (AA) or glioblastoma multiforme (GM), recurrent after maximal radiotherapy and/or surgery, were initially treated on an institutional protocol of Tamoxifen (TAM) 120 mg/m^2 b.i.d. Unfortunately, nine patients progressed; performance status (PS) deteriorated in all; CT scans showed increased size and enhancement. Because of the suggestion of increased enhancement, TAM was continued; concurrent BCNU 240 mg/m^2 q 8 weeks was initiated. Durable clinical responses, with significant PS improvement, and CT scan responses are produced. Serial MR Spectroscopic imaging documented persistent elevation of lactate and lipid resonances in non-responders, compatible with persistent tumor viability. In responders, lactate and lipid resonances increase transiently (compatible with a shift to anaerobic metabolism and cell membrane degradation) and then decrease significantly within two months of BCNU initiation (compatible with removal of cellular debris).

Patient #	A	B	C	D	E	F	G	H	I
Grade	GM	AA	AA	GM	GM	AA	GM	GM	GM
Age	45	42	42	56	43	41	43	44	48
Sex	F	M	M	M	M	F	M	F	M
Month to progression (prog.) on TAM	2	7	2	1	2	1	½	1	½
Radiologic response to TAM/BCNU	Prog.	MR	MR	Prog.	PR	PR	MR	Prog.	SD
Clinical response to TAM/BCNU	none	excellent	moderate	none	stable	excellent	excellent	none	moderate
Response duration	0	12+	11+	0	8+	8+	8+	0	5+
Survival	3	12+	11+	2	8+	8+	8+	2	5+

PROGNOSTIC VARIABLES OF SURVIVAL IN GLIOBLASTOMA MULTIFORME PATIENTS BASED ON PREOPERATIVE MRI DATA. M.A. Hammoud, R. Sawaya, W. Shi, P.F. Thall, N. Leeds, U. T. M. D. Anderson Cancer Center, Houston, Texas

Tumor necrosis, enhancement, and associated edema in patients with glioblastoma multiforme (GBM) represent biological variables that can be quantitated on preoperative MRI scans. We reviewed 48 highly selected patients all of whom had lobar lesions, underwent gross total tumor resection, and received adjuvant treatments (radio and chemotherapies). None of these patients had surgery for recurrent tumor resection and none had multifocal tumors. The median age was 50 years. The median Karnofsky performance score was 80. Multivariate analysis using the Cox model revealed that the strongest prognostic variable is the amount of tumor necrosis on preoperative scan ($P<0.001$) with a median survival of 42, 24, 15, and 12 months for tumor necrosis grades of 0 (7 pts.), I (11 pts.), II (9 pts.), and III (21 pts.) respectively. The intensity of enhancement of tumor nodule is another prognostic factor ($P = 0.003$) with median survival of 35, 18, and 13.5 months for enhancement grades of 0 (2 pts.), I (22 pts.), and II (24 pts.) respectively. The extent of peritumoral edema has a quadratic effect ($P = 0.003$) with grades I (19 pts.), II (22 pts.), and III (7 pts.) surviving for 24, 12, and 20 months respectively. Location and volume of tumors were not statistically significant predictors of survival ($P>0.05$). In conclusion, GBM patients with little or no necrosis and with less tumor nodule enhancement on preoperative MRI survive longer than patients with greater amount of necrosis and greater degree of tumor nodule enhancement. In addition, moderate degree of peritumoral edema is associated with worse prognosis.

MRI OF THE CAUDA EQUINA IN THE PARANEOPLASTIC ANTI-HU SYNDROME
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Objective: We report a patient with a paraneoplastic, Anti-Hu syndrome whose MRI shows gadolinium enhancement of the cauda equina.
Background: Abnormal enhancement of the cauda equina on MRI following gadolinium administration is seen in patients with leptomeningeal disease due to carcinomatosis or lymphomatosis but has never been described in patients with a paraneoplastic syndrome.
Case Presentation: A 58-year-old woman presented with progressive lower extremity weakness and mild intermittent numbness. Examination revealed weakness (prox > distal), loss of achilles reflex intact vibration and proprioception with mildly decreased pin prick and temperature. Cerebrospinal fluid x 4 was normal except for mildly elevated protein (106 mg/dl) and IgG, synthesis rate. Electrophysiologic studies provided evidence of multiple lumbosacral radiculopathies with acute axonal injury. MRI of lumbar spine (1.5 tesla Picker) was performed five weeks after onset of weakness. High CSF and serum anti-Hu antibodies were established by immunohistochemical and Western blot assays. CT of the chest, followed by bronchoscopy revealed a right upper lobe small cell undifferentiated lung carcinoma.
Results: T1 weighted gadolinium studies revealed enhancement of individual nerve roots within the thecal sac extending from L2 to S1.
Conclusions:
1) The first reported case of paraneoplasia related MRI changes involving the lumbosacral nerve roots probably representing increased permeability in the blood-nerve barrier due to autoantibody "inflammation."
2) Electrophysiologic studies support a clinical diagnosis of an Anti-Hu cauda equina syndrome (polyradiculopathy) without evidence of ganglionitis (sensory neuronopathy). Although the patient may eventually develop a paraneoplastic sensory neuronopathy (PSN), this initial presentation is uncommon.
3) After treatment with lumbosacral radiation and chemotherapy, patient's neurological condition improved significantly. Because neurologic improvement in an Anti-Hu syndrome rarely occurs, the therapeutic effects of radiation therapy must be further investigated.

INTRAVASCULAR MALIGNANT LYMPHOMATOSIS (IML) PRESENTING AS A SPINAL CORD SYNDROME. M. Patel, B. Truax, P. Kinkel, K. Shin, L. Mechtler, Dent Neurologic Institute, Roswell Park Cancer Institute, SUNY at Buffalo

Objective: To describe three cases of IML with predominant features of a myelopathy, including neuroimaging studies.

Background: IML is a rare, fatal intravascular form of Non-Hodgkin lymphoma with a particular affinity for the CNS. 62 patients with neurologic involvement reported in the English literature, including 3 of our own, were reviewed. 84% had global encephalopathy, 76% focal neurologic deficits and 45% had evidence of a myelopathy. Systemic symptoms include fever (55%), malaise (43%), and weight loss (16%). Laboratory studies revealed an elevated LDH (86%) and ESR (76%), as well as a low grade anemia (30%). CSF was non-diagnostic except for a mild to moderate elevation of protein (87%) and mild pleocytosis (36%).

Methods:
Three cases presenting with myelopathy associated with focal neurologic deficits and a decline in cognition were reviewed. LDH was elevated in all patients, while 2 patients had anemia and elevated sedimentation rate. MRI of the lumbar spine demonstrated an elliptical shaped conus tumor that enhanced with contrast. MRI of the brain revealed multiple subcortical areas of long T_2 (hyperintensity) that appeared consistent with infarctions. Pathology confirmed IML in all patients. Course of the disease despite therapy (radiation, steroids) was progressive with a mean survival time of 8 months, similar to the MST in literature (7 months).

Result: IML, although a multisystem disease, may cause spinal cord symptoms in one fourth of cases. MRI of the spine is the most sensitive study, but non-specific.

Conclusion:
The diagnosis of IML must be entertained in a patient presenting with multifocal neurologic deficits including myelopathy. Elevated ESR, LDH as well as low grade anemia compliment the diagnosis.

CHRONIC MENINGITIS: THE ROLE OF MENINGEAL OR CORTICAL BIOPSIES IN THE MAGNETIC RESONANCE IMAGING (MRI) ERA

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Meningeal and cortical biopsies were evaluated in 37 patients with chronic meningitis of unknown cause occurring in the MRI era (1985-1993). Included were 25 men and 12 women (mean age of 54 years). MRI with gadolinium contrast was the most useful diagnostic imaging technique, demonstrating meningeal enhancement in 15 of 32 patients (47%). Only 2 of 32 (6%) computed tomography (CT) scans revealed enhancement. A definitive diagnosis was made in 16 of 41 biopsies (39%), but in cases wherein enhancement was present on either MRI or CT a diagnosis was obtained in 80% (12 of 15 cases). Only 2 of 22 biopsies (9%) from non-enhancing regions were diagnostic. Although the locations of enhancement were distributed evenly, biopsies through suboccipital and pterional craniotomy gave highest diagnostic yields (50%). Furthermore, if the biopsies were obtained from enhancing regions, the yield of these approaches increased to 84% and 100%, respectively. Of 18 cases wherein both meninges and cortex were biopsied, only one had cortical involvement alone. The meninges were therefore diagnostic in 15 cases (94%). Second biopsies were necessary in 4 cases of which the 3 biopsies from enhancing regions were diagnostic. The most frequent causes of chronic meningitis were sarcoid (31%) and metastatic adenocarcinoma (25%). We conclude that a) MRI is the preferred imaging technique, b) biopsy of an enhancing region is most likely to be diagnostic, c) posterior fossa or pterional approaches give the highest diagnostic yield, and d) that cortical biopsy, though helpful for preserving structural integrity of the overlying leptomeninges, may be unnecessary and should be individualized.

MEDULLOBLASTOMAS IN LATE MIDDLE AGE AND THE ELDERLY: REPORT OF TWO CASES.

D A Ramsay[1], J Bonnin[2], D R Macdonald[1], L Assis[1]. [1]Victoria Hospital, LONDON, Ontario, Canada; [2]Methodist Hospital of Indiana, INDIANAPOLIS, IN, USA.

Background: Although 15% to 36% of medulloblastomas occur in adults they are rarely described in patients in or beyond the fifth decade. Since there is only one detailed case description in the literature of a 'late onset medulloblastoma' (in a 73 year old woman - J. J. Kepes et al, Neurosurgery 21:81-83, 1987), two medulloblastomas occurring late in life are characterized in this report.

Case Summaries: Case 1 was a 66 year old male and Case 2 a 65 year old female. The preoperative diagnosis based on MRI findings in each case was a cerebellar metastasis but neither patient had a known primary source. CSF dissemination had occurred in Case 1. 'Gross total resection' of a desmoplastic, glial fibrillary acidic protein-immunolabellable tumour was performed in both cases. The first case was treated with craniospinal radiotherapy and chemotherapy and the second case received cranial radiotherapy only. An autopsy carried out on Case 1 22 months after surgery showed widespread bone marrow dissemination of the tumour and minimal evidence of local recurrence. There was no MRI evidence of recurrence in Case 2 17 months after surgical resection.

Conclusions: These cases exemplify the difficulty in making the rare diagnosis of medulloblastoma preoperatively in late middle age and the elderly. In the laboratory immunohistological markers and electron microscopy should allow the tumours to be distinguished from poorly differentiated metastatic tumours, particularly the small cell carcinoma of lung. Late onset medulloblastomas may arise from cerebellar heterotopias (incidental finding in 0.05% of adult autopsies) or be a poorly differentiated special type of astrocytoma.

MEDULLOBLASTOMA IN 48 ADULTS TREATED BETWEEN 1958-1988.

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Purpose: To assess the outcome and prognostic factors for adult patients with medulloblastoma managed by postoperative radiotherapy between 1958 and 1988 at the Princess Margaret Hospital.

Methods and Materials: A retrospective review was undertaken of 48 patients aged 16 years or older who received radiotherapy for medulloblastoma. The median age at diagnosis was 25 years, with 36 male and 12 female patients. Sixteen tumors were confined to midline structures, and 32 were localized to a cerebellar hemisphere or involved midline and lateral structures. The desmoplastic variant was reported in 12 cases. Complete macroscopic removal was achieved in 22 patients, subtotal removal in 23, and biopsy only in 3. Forty-six patients received craniospinal radiation and 2 patients received local irradiation only.

Results: Median overall survival was 7.9 years, and 5 and 10 year overall survival was 62% and 41% respectively. Significant factors for disease-free survival were M stage (M_0 vs M_{1-4}, p=0.0005), functional state at the time of radiotherapy (1-2 vs 3-5, p=0.0046) and the presence or absence of hydrocephalus preoperatively (p=0.0173). Twenty-four patients developed recurrent disease with 14 relapsing first in the posterior fossa. Subtotal removal of tumor (p= 0.04) was the only factor predictive of posterior fossa relapse.

Conclusion: Symptomatic patients (neurologic functional state 3-5) at the time of radiotherapy or those who present with hydrocephalus have poorer disease-free survival. Gross total resection improved posterior fossa control. Patients with disease outside the posterior fossa at diagnosis have a very poor prognosis.

TREATMENT OF LOW GRADE GLIOMAS IN THE CT SCAN ERA: A REVIEW:

JP Bahary*, JG Villemure#, S Choi@, R Leblanc#, A Olivier#, G Bertrand#, L Souhami*, D Tampieri and J Hazel* *Div of Radiation Oncology, Dept of Oncology, @Dept of Epidemiology and statistics and Dept of Neurosurgery, McGill University

An analysis of fifty-nine (59) patients with a diagnosis of low grade pure astrocytoma or mixed oligo-astrocytoma from 1974 to 1992 was performed. All patients underwent CT scan preoperatively, and all had a histological grade 1-2/4 (Kernohan classification). Patients with a histological diagnosis of pure oligodendrogliomas were excluded from this analysis due ot their better prognosis. There were 18 females and 41 males. Patient's age ranged from 12 to 73 years with a median age of 33. Fifteen (15) patients had a stereotactic biopsy as the only surgical procedure, 30 had a partial tumor resection and 14 a gross total tumor resection.

Thirty-nine patients received radiotherapy at time of initial diagnosis. Two received whole brain radiotherapy, 24 had whole brain irradiation followed by a boost and 12 had partial brain irradiation. In one case radiotherapy details were not available. Total dose ranged from 50-60 Gy with a median total dose of 59.4 Gy with daily fractions of 1.8 to 2 Gy. Median follow up was 54 months with a range of 4-214 months. Overall survival was 37% at 10 years and 25% at 15 years. Survival at 5 years for patients treated at initial diagnosis with surgery alone (Sx) was 66% vs 67.3% for patients treated with radiation (RT) at time of initial diagnosis.

There was a statistically significant survival difference according in younger patients (less than 35 years: p=0.032), extent of surgical resection (partial or gross total resection compared to biopsy only: p=0.003) and sex, with females doing better (p=0.044).

In conclusions survival for patients with low grade gliomas in the CT scan era seems to be improved compared to historical controls. As well, extent of surgery, patient's age and sex seems to impact on patient's survival.

GIANT ENCEPHALITIC TUMOR-LIKE DEMYELINATING LESIONS OF THE BRAIN W. Grand, R. Plunkett, F. Munschauer, P. Ostrow, L. Mechtler, K. Shin. Department of Neurosurgery and Radiation Oncology, University at Buffalo, Buffalo General Hospital, Roswell Park Cancer Institute

Demyelinating diseases of the brain, particularly multiple sclerosis, are known to show discrete, small periventricular demyelinating plaques on Magnetic Resonance Image. However, awareness of giant encephalytic demyelinating lesions could avoid needless radical surgical resection, radiation, or chemotherapy for a presumed malignant glioma. A 26 year old woman presented with a deep diffuse mass lesion in the centrum semiovale. Stereotactic biopsy confirmed a demyelinating encephalitic process which resolved spontaneously. A 60 year old man's whose condition, was confirmed on open biopsy, was gradually resolved as well. The etiology of these giant encephalitic processes are unknown.

Although the long term clinical course of this entity varies, recovery in the weeks and months after presentation is usual. The details of our two patients and reported cases in the literature are outlined.

DISSEMINATED NECROTIZING LEUKOENCEPHALOPATHY (DNL): A CASE REPORT. L P Hudson[1], L Assis[1], A L Cooke[2], R F Del Maestro[1], D R Macdonald[1,2], D A Ramsay[1]. [1]Victoria Hospital and [2]London Regional Cancer Centre, LONDON, Ontario, Canada.

Background: Amongst the many central nervous system complications of radiotherapy and chemotherapy DNL is a rare, fulminating, focally tumour-like, necrotizing white matter disease that occurs 5m to 10m after cranial radiotherapy in patients with haematopoietic malignancies who have received cytotoxic drugs (notably methotrexate), either systemically or, more typically, directly into the CSF, shortly before the disease becomes symptomatic (L. J. Rubinstein et al, Cancer 35:291-305, 1975). An example of this illness is described.
Case Summary: The patient, a 29 year old female, presented with a mediastinal T cell lymphoma. Despite systemic chemotherapy, meningeal and radiologically suspected multifocal cerebral invasion appeared 3 months later, which was effectively treated with cranial irradiation (5400 cGY) and intraventricular methotrexate and cytarabine. Six weeks after the final dose of intraventricular chemotherapy a large right frontal mass with multiple focal areas of enhancement at its margins was biopsied and shown to be necrotic tissue. The lesion did not respond to treatment and the patient died 10 months after presentation.
Pathological Findings: At autopsy widespread, viable, retroperitoneal and mediastinal lymphoma was noted. The diffusely and severely swollen brain contained a mass (grossly reminiscent of a glioblastoma) of coagulative necrosis in the callosal rostrum and bifrontal centrum semiovale whose edges scrupulously spared the grey matter and which contained focally numerous axonal swellings; vascular changes were not seen. Other smaller areas of similar necrosis were in the right occipital white matter, cerebral peduncles and pons.
Conclusions: DNL should be included in the differential diagnosis of a brain mass in a patient who has received cranial radiotherapy and 'intrathecal' chemotherapy. It occurs sooner than, and its gross and histological appearances are distinct from, the late delayed effects of brain irradiation ('radionecrosis'). The emergence of DNL may be related to the cytolytic effects of chemotherapy agents on oligodendroglia that are recovering from the transient 'early delayed' effects of radiotherapy.

TREATMENT OF MALIGNANT SUPRATENTORIAL GLIOMA IN OLDER ADULTS: OUTCOME ASSESSMENT. S. Meckling, O. Dold, P. Forsyth, P. Brasher, N. Hagen. Tom Baker Cancer Centre, Calgary, Canada.

The incidence of malignant supratentorial glioma is increasing in the geriatric population. Although there is a lower survival rate for aged brain tumor patients than younger patients, it is not clear whether this relates to tumor insensitivity to treatment modalities, to age-related comorbidity, or to other factors such as reluctance to treat based on age alone.

The purpose of this study is to assess the outcome of treatment of malignant supratentorial glioma in elderly adults in southern Alberta. The Alberta Cancer Registry was used to identify all patients aged 70 years or more from Southern Alberta diagnosed with supratentorial malignant glioma between 1978 and 1992. Survival and improvement in level of function were correlated with surgical treatment, radiation therapy, performance status, pretreatment imaging studies, and other variables. 99 patients fulfilled entry criteria and had sufficient clinical information available. 56 patients completed radiation therapy; 10 did not because of declining performance status during radiation therapy. 33 were not offered radiation therapy, 16 because of poor level of function, 5 because of age, and 14 for other reasons. Median survival of all patients was 3.2 months.

These preliminary results suggest survival is poor in aged adults with supratentorial malignant glioma because of poor initial level of function or declining level of function despite radiation therapy. Further analysis will attempt to identify pre-treatment patient-related factors which predict poor or good outcome.

GENDER AND MALIGNANCY IN PRIMARY BRAIN TUMOURS Muller PJ, Tucker W, Moulton R, Cusimano M and Bilbao J, St. Michael's Hospital, University of Toronto, Toronto, Ontario.

It has long been recognized that primary malignant brain tumours have a male proponderence and that benign meningiomas are more common in the female population. We examined the relationship between gender and pathology in a series of gliomas and meningiomas diagnosed at St. Michael's Hospital from 1980 to 1991.

Of 871 astrocytic tumours with a mean age of 55+12 years 180 were low grade astrocytoma [grade 2], 328 were malignant astrocytomas [grade 3] and 363 were glioblastoma multiforme [grade 4]. The male/female ratios were 1.25, 1.39 and 1.56, respectively [$p < 0.005$].

Of 376 meningiomas with a mean age of 58+14 years 23 were histological malignant or atypical. The male/female ratio was 1.091 in comparison to 0.423 for the benign meningiomas [$p < 0.05$].

There does appear to be a relationship between the degree of histologic malignancy and gender.

PLEOMORPHIC XANTHOASTROCYTOMA: A PROPOSAL FOR TWO CLINICOPATHOLOGIC SUBTYPES.

P A Pahapill[1], R F Del Maestro[1], D A Ramsay[1], [1]Victoria Hospital, London, Ontario, Canada.

Background: Pleomorphic xanthoastrocytoma (PXA) is a recently characterized neoplasm that has been added to the new WHO classification of tumors. The predominant histological features of PXA are cellular pleomorphism, lipid droplets in the tumor cell cytoplasm and abundant reticulin fibres in the stroma. Mitoses are occasionally seen but necrosis is rare. The clinical features are: 1) occurrence in young patients; 2) a superficial location in the cerebrum; and 3) a good prognosis. Although there is a concensus on the status of PXA as an entity, the biological behaviour of some of these is less predictable. We propose the existence of two subtypes of PXA, each with distinct clinical pathological characteristics. This classification aids in predicting clinical outcome.
Methods: Two new cases of PXA are presented, each illustrating the clinical pathologic characteristics of the proposed subtypes. In addition, a literature review of over 70 cases is provided.
Results: Pathologically, the benign subtype (I) of PXA could be distinguished by the absence of mitotic figures and lack of necrosis. Type II PXA (aggressive) was associated with increased mitotic activity and areas of necrosis. About 90% of Type I patients had initial symptoms in the first and second decades of life, while symptoms referred to Type II PXA occurred in the third and fourth decades. There was no sex predominance. Type II PXA presented either as a transformation from Type I PXA (2/3) or as an initial finding (1/3). Approximately 90% of Type I patients followed for more than 15 years were living after initial diagnosis and surgical treatment. Recurrences occurred in approximately 25% of patients usually after 15 to 20 years from initial diagnosis. Most recurrences were of the Type II variety carrying only a 2 to 3 year prognosis.
Conclusions: From the currently reported cases on PXA, there is data to support two subtypes of PXA. Type I (benign) is characterized by fewer mitoses and no areas of necrosis with a favourable prognosis. Type II (aggressive) is characterized by increased mitotic activity and areas of necrosis with a less favourable prognosis. It is likely that Type I has the potential to transform into Type II PXA.

THE NEURO-ONCOLOGICAL PATHOLOGY OF STEREOTACTIC RADIOSURGERY.

D A Ramsay[1], R F Del Maestro[1], B Fisher[2], W Pexman[1], J Taylor[2], T Lee[3], [1]Victoria Hospital, [2]London Regional Cancer Centre and [3]St. Joseph's Health Care Centre, London, Ontario, Canada.

Background: The treatment of primary and secondary brain tumors by whole brain radiotherapy is compromised by the need to curtail radiation doses to prevent injury to surrounding intact nervous tissue. The development of stereotactic radiosurgery (SR) has allowed the use of single high dose radiation treatments to brain tumors which minimizes irradiation to uninvolved neuroparenchyma. Little information is available on the histological effects of single high dose radiation on human brain tumors.
Methods: At this centre, the histological features of the following neoplasms have been studied (time from SR in parenthesis): 1 excised metastasis (1y), 2 excised recurrent glioblastomas (both 3 months) and 3 autopsied cases of high grade gliomas (7 weeks, 3.5 and 5 months). All gliomas had recurred after whole brain irradiation and chemotherapy before being treated with SR.
Results: The metastasis showed multifocal microscopic sites of tumor recurrence, dural invasion, extensive desmoplasia and vascular changes reminiscent of the 'late delayed effects' of irradiation; the adjacent white matter was rarefied and its astrocytes showed a greater degree of nuclear atypia than is usually associated with 'lower dose' radiation leukoencephalopathy. The three fatal cases of malignant glioma showed large areas of bland necrosis at the site of irradiation, vascular changes that did not differ from 'normal' tumor vasculopathy and one case of fatal hemorrhage. Dynamic CT imaging demonstrated decreased tumor blood flow and blood volume in one surviving case and the resected tumor showed large areas of geographic or confluent necrosis and histologically healthy perivascular tumor cells. The second surviving patient had increased tumor blood flow and blood volume and pathologically recurrent tumor.
Conclusions: This limited series suggests that a slightly wider than image target may improve results in SR treatment of metastasis but with a risk of local white matter injury. In high grade gliomas, SR kills tumor cells but the efficacy of SR in these infiltrative tumors must await the completion of present multicentre trials.

THYROID DOSES DUE TO RADIOSURGERY OF THE BRAIN

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Radiosurgery is used to treat a variety of benign and malignant tumors. One of the associated concerns is thyroid cancer from external radiation given to children under 5 years of age. A complete treatment simulation of clinical cases was done using an Alderson phantom. The doses were measured for different cone sizes and target positions using thermoluminescent dosimeter and a solid state dosimeter. The results indicated that the thyroid doses were done to the sagittal plane and that a cerrobend collar shield did not reduce the doses. The doses were related to the field size at the isocenter. 6.6 cGy for 18.5 mm and 11 cGy for 35.2 mm reduced rapidly when the impact was displaced to 2.0 cm. However, when the target is laterally displaced, the eye dose increases, about 32 cGy for the larger field size at 2.0 cm from the midline. In order to reduce the thyroid doses to a minimum, it is recommended to eliminate the sagittal plane of rotation wherever it passes through the midline of the brain.

BLACK BRAIN ON CT: AN EFFECT OF BRACHYTHERAPY?

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"Black brain" refers to an abnormality on CT characterized by extensive hypodensity on plain and enhanced scan occupying more than 50% of a cerebral hemisphere, in the absence of enhancing tumour. We have observed it on CT post brachytherapy in a significant number of patients and describe the imaging and clinical features.
Nine of the 53 patients randomized to receive brachytherapy as part of the initial therapy for malignant astrocytoma developed "black brain". None of the patients with new malignant astrocytoma randomized to receive standard therapy without implant developed "black brain". Two of 10 patients implanted for recurrent single brain metastasis developed "black brain".
The majority of the patients exhibited progressive neurological deterioration (ie. hemiparesis) in the apparent absence of recurrent tumour on imaging. Only two of the patients with malignant astrocytoma survived longer than the median survival for the overall group. The two patients with metastatic tumours lived longer than the median. Autopsy of one patient with malignant astrocytoma revealed demyelination, no identifiable tumour cells, and no evidence of significant vasculopathy.
We conclude that: (1) the abnormality of "black brian" appears to be commoner in patients receiving brachytherapy than a randomized matched control group receiving standard therapy without brachytherapy; and (2) "black brain" may be associated with significant hemispheric dysfunction and neurological loss, but it is not clear whether this is a cause or effect relationship.

BRAIN TUMORS TREATED WITH STEREOTACTIC RADIONUCLIDE INJECTION

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From January 1988 to April 1992, 230 brain tumors were treated with stereotactic injections of radionuclides, phosphorus-32(32P) and yttrium-90(90Y). These patients aged from 2.5 to 70 years (average 38 years), 102 were male and 128 were female. The tumors were located in the deep part or functionally critical area of brain. Astrocytoma was found in 114 cases, craniopharyngioma in 81, metastatic carcinoma in 15, germinoma in 11, meningioma in 5 and pituitary adenoma in 4. After 387 times of colloidal isotopes injection, no major adverse effects or complications occurred. Follow up for 6 to 48 months showed the improvement of symptoms in 175 (76%) patients and CT scans confirmed the diminished tumors. We consider this method is safe, simple and effective for the treatment of some brain tumors.

5-FLUOROURACIL PLUS HIGH DOSE FOLINIC ACID FOR RECURRENT GLIOMAS. D.J. Stewart, Ottawa Regional Cancer Centre, Ottawa, Ontario, K1Y 4K7, Canada.

We treated 14 patients with gliomas recurrent after cranial radiation ± 1 prior chemotherapy regimen on a phase II study of 5-fluorouracil (FU) plus high dose folinic acid (FA) daily x 5 every 4 weeks. There were 8 males and 6 females. Median age was 47 years (range, 35-71). Median ECOG performance status was 2 (range, 1-3). Prior chemotherapy included PCV in 7 patients, CCNU in 1, cisplatin + mitomycin in 2, & none in 4. All patients had prior radiation. Median time from last chemotherapy was 8 months (range, 1-16), median time from radiotherapy was 27 months (median, 2-130), and median time from diagnosis was 31 months (range, 5-133). Tumor types were glioblastoma in 7 patients, grade II astrocytoma in 4, oligodendroglioma in 2 and oligoastrocytoma in 1. The first patient received FU 370 $mg/m^2/day$ + FA 200 $mg/m^2/day$. FU was ↓ to 300 $mg/m^2/day$ in later patients due to excess toxicity. Nine patients received 1 course, 3 received 2, and 1 received 16. One patient was inevaluable for response and 2 are too early to evaluate. One patient with an oligoastrocytoma that had recurred with a contrast enhancing mass after prior radiation & PCV had a partial remission, with complete resolution of CT enhancement & mass effect, improvement of symptoms, but residual calcification. Her tumor recurred 3 months after stopping chemotherapy (after 12 courses), and responded to reinitiation of FU + FA. She has now had 16 courses, and continues on treatment 21 months from initial FU + FA (86 months from diagnosis). All other patients failed. Median survival for all patients from start of FU + FA was 3 months (range, 0.5-20+). The 1st patient had febrile neutropenia, thrombocytopenia, grade 4 stomatitis & esophagitis, & dehydration. In the 10 evaluable at lower doses, toxicity included granulocytopenia (2), grade 1-2 stomatitis (4), diarrhea (5), nausea (1), fatigue (2), hiccups (1), & rash (1). Hence: FU + FA has at best modest activity in previously treated gliomas. Supported in part by Burroughs Wellcome Canada.

PRE-RADIATION CHEMOTHERAPY FOR MALIGNANT GLIOMA: *S. Kirby, D.R. Macdonald, B.J. Fisher, J.G. Cairncross. London Regional Cancer Centre, London, Canada.*

We investigated the efficacy of chemotherapy (CTX) prior to radiation (RT) for malignant gliomas. Twenty-nine patients (Karnofsky score >60) were treated with at least one cycle of PCV (procarbazine, CCNU and vincristine) or CCNU before RT (6000 cGy). Response to CTX was assessed independently of RT using rigorous criteria. Eighteen patients with glioblastoma (62%) received PCV (14 patients) or CCNU (4). Three had partial responses, 7 were stable, 6 progressed, and 2 with complete resections did not progress. Four progressive cases stabilized with RT and 2 continued to progress. Seven with anaplastic astrocytomas (24%) received PCV (6 patients) or CCNU (1). Four were stable, 1 progressed (this patient did not stabilize with RT), and 2 with complete resections did not progress. Four with anaplastic oligodendrogliomas or anaplastic mixed gliomas (13%) received PCV. One had a partial response and 2 were stable and one with complete resection did not progress. Overall, 4 had partial responses (14%), 13 were stable (45%), 7 progressed (24%), and 5 with complete resections did not progress (17%). Four of 7 patients who progressed on CTX stabilized with RT. Toxicity was mainly hematologic and tolerable. We conclude that one cycle of CTX prior to RT is well tolerated by most patients and allows an objective assessment of response to CTX in many. Follow-up and further experience are needed.

PRESERVATION OF VITAL NEURAL STRUCTURES WITH CT/MRI-BASED 3-DIMENSIONAL CONFORMAL RADIOTHERAPY FOR LARGE PITUITARY MACROADENOMAS.

W Roa, B McClean, S Buckney, S Halls, S Richardson, RC Urtasun, Cross Cancer Institute, Edmonton, Alberta, Canada.

Radiotherapy for large pituitary macroadenomas located close to vital neural structures is problematic due to the high risk of radiation injury. We believe that CT/MRI-based 3-dimensional conformal radiotherapy (3D-CRT) can improve tumor volume coverage and hence spare the dose to nearby vital structures. Three consecutive patients with gross residual pituitary macroadenomas and partial visual defects had CT and MRI performed in the treatment position with a CT/MRI-compatible immobilization head shell. 3D-CRT treatment planning using CT/MRI contour volumes, beam's eye view displays and conformal blocks, as well as conventional treatment planning using the regular simulation process, were performed independently. The separate plans were assessed for planning target volumes (PTVs), dose distributions in the PTVs, and dose distributions in the individual vital neural structures. A radiologist independently evaluated the plans for possible sites of geographical miss. The 3D-CRT plans produced smaller PTVs with an average reduction of 30% and improved target dose distributions. Absorbed doses to the various adjacent vital neural structures were reduced by at least 50% of those for the conventional treatment planning. Geographical miss was also noted to be 30% more likely in the conventional plans. This study provides a dosimetric basis for a phase I/II clinical trial comparing conventional and 3D-CRT treatments for large pituitary macroadenomas. Supported by Alberta Cancer Foundation.

PHOTODYNAMIC THERAPY OF RECURRENT CEREBRAL METASTASES

Muller PJ and Wilson BC, St. Michael's Hospital and Princess Margaret Hospital, University of Toronto, Toronto, Ontario.

Ten patients with metastatic cerebral tumours were treated with PDT. There were 5 males and 5 females; the mean age was 57+11. The median Karnofsky score was 72+15. There were 5 primary lung cancers, 2 breast, 1 colon and in 2 patients the primary was unknown. Photofrin 2 mg/kg i.v. was administered 12-24 hours prior to surgery. All had the tumour resected at craniotomy. The tumour resection was grossly complete in all but one patient leaving a cavity the walls of which consisted of edematous white matter. Intra-operative cavitary photo-illumination was carried out. The mean+sem tumour cavity volume was 15+3 cm^3. The mean+sem light energy administered was 1780J ± 560 and the mean energy density was 60+16 J/cm^2.

Histological assessment of the resection cavity which consisted of white matter grossly devoid of tumour revealed residual islets of tumour within the neuropil.

The median survival was 26 weeks post PDT with a range of 6 to 134 weeks. One patient is alive at 31 weeks post PDT and 3 lived longer than 1 year post PDT. Both patients who lived less than 30 weeks post PDT had advanced systemic diseases. There were no postoperative deaths. One patient displayed worsening of his hemiparesis. There were no systemic reactions to Photofrin and no cutaneous toxicities.

Further study of PDT in the treatment of recurrent post radiation cerebral metastases is indicated.

PHOTODYNAMIC THERAPY OF RECURRENT GLIOMAS

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Fifty patients with recurrent gliomas who had failed radiotherapy and who were candidates for palliative re-operation were treated with photodynamic therapy (PDT). There were 30 males and 20 females; their mean age was 40+13 and the mean Karnofsky score was 78+15. The number of gbm, malignant astrocytomas and other gliomas was 27, 15 and 8, respectively. Five of the glioblastomas arose from lower grade tumours. All patients received Photofrin 2 mg/kg i.v. 12-36 hours prior to tumour resection and cavitary photoillumination with 630 nm light produced by an argon pumped dye laser. The median photic energy was 1755 J and the median energy density was 45 J/cm^2.

There were 2 post-operative deaths; one secondary to an intracerebral hemorrhage into the tumour cavity and the other from a pulmonary embolism.

The median survival for this recurrent group from PDT was 7.2 months and the 1 and 2 year survival rates were 31% and 19%, respectively; and, the median survival from first operation was 27 months with 1 and 2 year survival rates of 84% and 60%, respectively. The median survival for the 27 recurrent glioblastoma patients from PDT was 6.1 months with a 1 year survival rate of 16%; and, the median survival from first operation of the 22 patients with an initial diagnosis of gbm was 20 months with 1 and 2 year survival rates of 84% and 60%, respectively. Further trials with higher light doses are being developed.

HEALTH CARE BUDGET CUTS: WILL LESS FREQUENT CT OR MRI SCANS JEOPARDIZE OUR PATIENTS WITH MALIGNANT BRAIN TUMOUR? Chuah CTH, Fulton, DS, Urtasun, RC Cross Cancer Institute, Edmonton, Alberta Canada

Systematic follow-up of patients with primary malignant brain tumor is intended to identify tumour response, recurrence and side effects of therapy. Assessment involves repeated neurological examination and CT or MRI. The neurological examination is indispensable in the clinical care of patients but does not exclude tumour recurrence. The early detection of tumour recurrence allows therapeutic intervention before major neurological dysfunction occurs and may improve quality of life by preventing or delaying neurological deterioration and reducing the need for Dexamethasone. It is not known whether or not detection and treatment of recurrences when they are asymptomatic prolongs time to tumor progression (TTP) or survival time (ST). Recent budget cut have resulted in the need to reduce the frequency of routine follow-up scans in patients with brain tumour.

All patients with primary malignant brain tumour with documented first intracranial recurrence treated between 28 March 1991 and 1 February 1994 were included in this retrospective study. TTP and ST for patients asymptomatic at the time of first progression were compared to TTP and ST for symptomatic patients. TTP and ST for patients with short scheduled follow-up intervals prior to first progression were compared to TTP and ST for patients with longer follow-up intervals.

TTP and ST were significantly longer for asymptomatic patients than for symptomatic patients. The data on TTP and ST following treatment of first progression for patients who had short vs long follow-up intervals prior to first progression was conflicting.

Conclusion: Early detection of asymptomatic recurrence by routine CT or MRI, followed by appropriate therapy, may prolong TTP and ST of patients with primary malignant brain tumour. Shorter follow-up by itself is of no benefit unless it results in detection of asymptomatic recurrence.

ASSESSING THE GLOBAL HEALTH STATUS OF PATIENTS WITH BRAIN TUMOURS USING A MULTIATTRIBUTE SYSTEM. A.C. Whitton, R.D. Barr, H. Rhydderch, T. Case, D. Feeny, W. Furlong, G.W. Torrance, Hamilton Regional Cancer Centre & McMaster University, Hamilton, Canada.

Increasing survival rates, particularly in paediatric oncology, have focused attention on the morbidity of therapy and the long-term effects of the disease and its treatment. There is little literature about the global health status of survivors of brain tumours, especially taking into account combinations and severity of sequelae. A comprehensive system has been devised for classifying the health status of patients, consisting of seven attributes: sensation, mobility, emotion, cognition, self-care, pain and fertility. Three to five levels of functioning are defined for each attribute and a combination of seven attribute levels constitutes one health state of 24,000 possible. The system has been used to classify the health status of children after treatment for high risk acute lymphoblastic leukaemia, Wilms' tumour, advanced neuroblastoma and brain tumours, with the last experiencing the most morbidity, as might be expected. A self-administered questionnaire has now been developed from which the overall health status of the patient can be determined, according to the same multiattribute classification system. The questionnaire has been used recently in the adult neuro-oncology clinic and we report the global assessment of morbidity burden from the perspective of the patients (with the help of relatives when necessary), compared with the general population.

BRAIN TUMOR ASSESSMENT INDEX

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One of the important prognostic factors in the management of malignant brain tumors is the functional performance status. In the RTOG/ECOG Study, patients with malignant astrocytoma and a Karnofsky performance score of 70-100 had a median survival of 12 weeks, and 34% survived 18 months. Unfortuneately, the Karnofsky Performance score is too crude to monitor the functional status of patients undergoing or having undergone treatment. This new Index is to combine all the clinical aspects and candidates at the time of assessment to provide an instrument to monitor patients status throughout their course of illness. Five major parameters are shown below.

The perfect score is 50 which indicates normal condition and as the patient develops symptoms, signs, and complications, the score reduces down to 10. As the condition improves, so does the score. This is simple, easy, practical and sufficiently semisensitive in monitoring the patients condition.

Assessment Index

Performance		**Neurological Finding**		**Decadron**	
Normal	10	Normal	10	None	10
Minor symptoms	8	Minor	8	<2 mgm/d	8
Unable to work	6	Moderate	6	2-8 mgm/d	6
Disabled	4	Severe	4	8-16 mgm/d	4
Very sick	2	Comatose	2	>16 mgm/d	2

Complication of Tx		**MRI/CT Scan**	
None	10	Normal	10
Mild	8	Diameter > 2.0 cm	8
Moderate	6	> 2-4 cm	6
Severe	4	> 4-8 cm	4
Life Threatening	2	Multiple	2