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Select Review in Neuro-Oncology

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Volume: 1, Issue: 1

Title: Graphic Analysis of Microscopic Tumor Cell Infiltration, Proliferative Potential , and Vascular Endothelial Proliferation

Review Type: Article

Category: Adult Neurosurgery

Journal: Surgical Neurology, Vol: 51, No. 3: pages 292-299, March 1999

Authors: Nagashima G, et. al.

Summary: These authors explore the microscopic and gross extent of tumor (GBM) as determined by pre- and post-mortem MRI, cell proliferation markers (Ki-67) and vascular proliferation, and attempt to correlate them graphically. They found: microscopic invasion beyond the area of increased signal on T2W MR images; heterogeneity in the distribution of Ki-67 which did not correlate to the areas of highest histologic malignancy or gadolinium enhancement; high expression of vascular endothelial growth factor (VEGF) in normal astrocytes beyond the established extent of tumor invasion. Their analysis was performed on a single autopsy brain.

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Volume: 1, Issue: 1

Title: Report of 190 consecutive cases of large acoustic tumors (vestibular schwannoma) removed via the translabyrinthine approach

Review Type: Article

Category: Adult Neurosurgery

Journal: Journal of Neurosurgery, Vol: 90, No. 4: pages 617-623, April 1999

Authors: Lanman TH, Brackmann DE, et al.

Summary: This article from the House Ear Institute summarizes a 5 year surgical experience with 190 large (> 3cm.) acoustic neuromas operated on via a translabyrinthine approach. In this surgical approach any residual hearing is lost, although for these large tumors hearing preservation is extremely unlikely with any form of treatment. In 36% of the cases the tumors were 4 cm or larger. The average hospital stay was 7.9 days, with 87% of patients leaving the hospital within 10 days. In 96.3% of cases, the surgeon's impression was that complete tumor removal was accomplished (no imaging documentation). Facial nerve function was excellent (Grade 1 or 2) in 52.6% and poor in 18.9% at 1 year follow-up. Transient CSF leak (14.2%), cerebellar ataxia (12.6%) and rehospitalization (7.4%) were the most common complications. In the discussion the authors go on to review the advantages of the translab approach over others, which include : early identification of the facial nerve, minimal retraction of the cerebellum, improved patient and surgeon position and adequate exposure. Other topics reviewed include facial nerve preservation, hearing preservation and postoperative complications. The authors conclude that the results with this surgical approach for large tumors > 3 cm., and for smaller tumors where hearing preservation is not an issue, are acceptable and they continue to recommend it. These tumors are also of a size felt by most radiosurgeons to be too large to treat safely. The report from this highly experienced surgical group will serve as a benchmark for others in the future.

Select Review in Neuro-Oncology

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Volume: 1, Issue: 1

Title: Differential effects of octreotide treatment and transsphenoidal surgery on growth hormone binding protein levels in patients with acromegaly.

Review Type: Article

Category: Adult Neurosurgery

Journal: Journal of Neurosurgery, Vol: 90, No. 4: pages 647-650, Apr. 1999

Authors: Hernandez I, Soderlund D, et al.

Summary: The treatment of patients with growth hormone (GH) secreting pituitary tumors (acromegaly) can involve medical, surgical and radiation treatments. Monitoring the effectiveness of these therapies has relied in the past on random serum GH levels, glucose suppression of serum GH levels and random insulin-like growth factor I (IGF-I) and insulin-like growth factor binding protein-3 (IGFBP-3). Growth hormone binding protein (GHBP) represents the extracellular portion of the GH receptor and serum levels are a reflection of tissue receptor status. Serum levels of GHBP are decreased in patients with active GH secreting tumors. Octreotide, a somatostatin analogue given by subcutaneous injection 3 times day, suppresses GH release from tumors. In this study 7 patients with active, untreated acromegaly had serum GH suppression by oral glucose, GHBP, IGF-I, and IGFBP-3 levels measured at baseline, 2 months after octreotide treatment and 1 month after transsphenoidal surgery. Octreotide therapy decreased levels of GH, IGF-I and IGFBP-3 and increased levels of GHBP, although none to normal levels. After surgery to remove the tumors, GHBP levels became normal especially in those patients whose GH levels were suppressed by oral glucose loading. In their discussion, the authors discuss the relationship between "big" and "big-big" GH in plasma (the latter referring to GH and GHBP aggregates) and the other serum markers they followed in this experiment. Their conclusion is that low GHBP levels in patients with acromegaly are normalized by surgery and correlate well with disease activity. The data presented support this and monitoring GHBP levels appears to offer another method of assessing the success of treatment in long term follow-up.

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Volume: 1, Issue: 1

Title: Radiotherapy in the Treatment of Benign Meningioma of the Skull Base

Review Type: Article

Category: Adult Neurosurgery

Journal: Journal of Neurosurgery, Vol: 90, No. 5: pages 823-827, May 1999

Authors: Nutting C, Brada M, et al.

Summary: This study reviews the results of external irradiation of 82 skull base meningiomas treated at the Royal Marsden Hospital between 1962-1992. A three field technique using mega-voltage linear accelerators was used and the median follow-up was 9 years (1 mo. - 27 yrs.). All but 11 of the tumors were located on the sphenoid wing or around the sella. The progression free survival (PFS) was 92% at 5 years and 83% at 10 years. Tumors arising in the parasellar region had better 10 year control rates than tumors of the sphenoid wing (90% vs. 69%). There was no difference in the tumor control of those patients treated after primary surgery versus those treated at recurrence. The overall 5 and 10 year survival rates were 83% and 71%. Toxicity of treatment was assessed in 61 of 82 patients. Visual impairment was noted in 6 patients: in 5 this was due to cataract formation and in 1 radiation retinopathy was identified. There were no cases of cranial nerve neuropathy or secondary brain tumor growth. The authors are correct in saying that these results, and others, will serve as a baseline for the evaluation of new treatment strategies such as radiosurgery and skull base operations.

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Volume: 1, Issue: 1

Title: Effects of clotrimazole on the growth, morphological characteristics, and cisplatin sensitivity of human glioblastoma cells in vitro

Review Type: Article

Category: Adult Neurosurgery

Journal: Journal of Neurosurgery, Vol: 90, No. 5: pages 918-927, May 1999

Authors: Khalid MH, Shibata S, Hiura T

Summary: Clotrimazole (CTZ) is an antimycotic that inhibits voltage and ligand stimulated calcium influx mechanisms in nucleated cells. It inhibits proliferation of normal cells by depleting intracellular calcium and preventing the rise in cytosolic calcium that normally follows mitogenic stimulations. Finally it is a cytochrome p450 inhibitor that can block epidermal growth factor (EGF)-stimulated DNA synthesis. The authors examined the effect of CTZ on 2 human glioblastoma cell lines, one (A172) with wild-type P53 and a second (T98G) with a mutant p53 gene. The authors found that CTZ inhibited the growth of glioblastoma cells in a dose dependent fashion. However, above 50-70 micromolar concentrations, CTZ caused significant cytotoxicity and cell detachment. The drug also caused morphologic changes of differentiation and the accumulation of cells in G0/G1 phase, and a decrease in cells in S phase. Measured by Western blot analysis CTZ increased GFAP and wild-type P53 expression, and decreased cellular c-myc and c-fos expression. The growth inhibitory effect of the drug was not overcome by EGF or c-myc peptide. Adding CTZ to cisplatin produced a synergistic effect on apoptosis for all concentrations of cisplatin tested. This study suggests that CTZ is an effective agent in inhibiting cell proliferation of glioblastoma cell lines in vitro. In addition, it causes morphologic changes suggesting differentiation, induces GFAP and wild-type P53 and downregulates c-myc and c-fos. It also has a synergistic effect with cisplatin and deserves more study as a potentially novel anticancer drug in treating glioblastoma.

Select Review in Neuro-Oncology

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Volume: 1, Issue: 1

Title: Treatment of intracranial gliomas with bone marrow-derived dendritic cells pulsed with tumor antigens.

Review Type: Article

Category: Adult Neurosurgery

Journal: Journal of Neurosurgery, Vol: 90, No. 6: pages 1115-1124, June 1999

Authors: Liau LM, Black KL, et al.

Summary: This is the second paper in this issue of the Journal of Neurosurgery on a method of enhancing cell mediated immunity as a method of controlling intracerebral tumor growth in an animal model. Dendritic cells are the most potent antigen presenting cells in the body. Precursors found in bone marrow can be stimulated by granulocyte-macrophage colony stimulating factor (GM-CSF) and interleukin-4 (IL-4). In this study dendritic cells pulsed ex-vivo were used to inhibit the growth of tumors within the CNS. Dendritic cells were isolated from sygeneic rat bone marrow after stimulation with GM-CSF and IL-4 for 8 days. After confirmation of the presence of functional dendritic cells in culture these cells were exposed for 16-24 hours to acid eluted peptides from either 9L glioma cells or normal astrocytes. One week after the intracerebral implantation of 9L cells into the rat brain, three weekly subcutaneous injections of dendritic cells pulsed with glioma peptides, non-pulsed cells, cells pulsed with antigens from normal rat astrocytes or control media were given. The survival of rats injected with dendritic cells pulsed with glioma antigens was significantly longer than those receiving non-pulsed cells, cells pulsed with normal astrocyte antigens or controls. Median survivals for the control media, unpulsed dendritic cells or normal astrocyte pulsed cells were 16, 17 and 22 days. In contrast, those rats receiving dendritic cells pulsed with 9L antigens had a median survival of 35 days ($P=0.027$). Immunohistochemical analysis of the brains of rats treated with pulsed dendritic cells showed an increase in perilesional and intratumoral infiltration of CD8+ T cells compared to other groups. This study has been well done with extensive documentation at each step of the experimental process. It suggests that there may still be a role for immunotherapy in the multidisciplinary approach to treating patients with malignant gliomas.

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Volume: 1, Issue: 1

Title: Gamma Knife Radiosurgery for Metastatic Melanoma: An Analysis of Survival, Outcome, and Complications

Review Type: Article

Category: Adult Neurosurgery

Journal: Neurosurgery, Vol: 44, No. 1: pages 59-66, Jan. 1999

Authors: Lavine SD, Petrovich Z, Cohen-Gadol AA, Masri LS, Morton DL, O'Day SJ, Essner R, Zelman V, Yu C, Luxton G, Apuzzo MLJ

Summary: In this article, investigators at the University of Southern California report their experience in treating patients with metastatic melanoma of the brain with gamma knife radiosurgery. Lavine et al treated 45 patients (78% male), with a mean age of 53 years, harboring up to 4 lesions, in 59 treatment sessions. The mean treatment dose was 21.6 Gy to the 56% mean isodose line. The median survival time was 43 months from diagnosis and 8 months from the time of gamma knife treatment. At the time of diagnosis, 78% of patients had known systemic disease, and 11% had seizures. 86% of lesions were cortical, 12% cerebellar, 1% pontine, and 1% thalamic. All patients were followed for a mean of one year. MRI scanning revealed a 97% local tumor control rate for the gamma knife-treated lesions, with 9 of 32 cases (28%) disappearing completely. 35/45 patients experienced either improved or stable neurological symptomatology. Only 2 patients died as a result of neurological disease. The authors concluded that gamma knife radiosurgery is a safe, noninvasive, palliative therapy for metastatic melanoma to brain, which may provide symptomatic relief of neurological symptoms in the majority of patients. The striking observation of this study was that despite the fact that only 2 of 45 patients received adjuvant whole brain radiotherapy (WBRT), which has been considered standard care in the past, only 6 patients developed new brain metastases during the study period. This report indicates that gamma knife radiosurgery is effective in treating lesions generally considered "radiation resistant", even in the absence of WBRT.

Select Review in Neuro-Oncology

<http://www.neurosurgery.org/tumor/selectreview/>

Volume: 1, Issue: 1

Title: Effects of continuous localized infusion of granulocyte-macrophage colony-stimulating factor and inoculations of irradiated glioma cells on tumor regression

Review Type: Article

Category: Adult Neurosurgery

Journal: Journal of Neurosurgery, Vol: 90, No. 6: pages 1064-1071, June 1999

Authors: Wallenfriedman MA, Conrad JA, et al

Summary: This paper examines the use of a cytokine, granulocyte-macrophage colony stimulating factor (GM-CSF), to stimulate an effective anti-neoplastic immune response in a syngeneic rat model of glioma. Clinically significant immune responses against glioblastoma multiforme (GBM) are rare for two important reasons. First, gliomas exhibit low immunogenicity, providing low levels of MHC I and other antigens necessary for recognition by the host immune system. Second, GBMs actively inhibit the patient's immune system via the production of immunosuppressive factors including transforming growth factor-beta2, interleukin-10, and PG-E2. T cells from GBM patients do not respond normally to stimulation with interleukin-2 (IL-2) due to low levels of a critical IL-2 receptor subunit, p55. GM-CSF stimulates the immune response by recruiting and activating dendritic and other antigen presenting cells. These cells can theoretically process tumor-specific antigens and induce an anti-tumor immune response. This study examines the potential of a continuous infusion of GM-CSF, along with intermittent subcutaneous injection of irradiated 9L gliosarcoma cells, to produce an anti-tumor response by providing recruitment and stimulation of APCs in the presence of 9L tumor. The authors studied several approaches to GM-CSF infusion/tumor antigen therapy, including demonstration of a dose response to therapy in contralateral flank tumors, demonstration that tumor antigen therapy or GM-CSF therapy alone were ineffective, and demonstration of immunity to tumor challenge as long as 8 months after initial treatment. Finally, they demonstrated that animals with intracranial 9L tumor inoculations were also relatively protected when given GM-CSF infusion therapy in conjunction with subcutaneous tumor antigen, with 2/5 long-term survivors as opposed to 0/5 in the control animals. Animals were treated without discernable toxicity. Effective anti-tumor immunotherapy has remained a largely elusive goal, despite numerous preclinical and clinical studies. Utilization of a non-IL-2 dependent immunostimulatory cytokine, in the presence of tumor antigen, may be a promising future approach for treatment of CNS tumors. Larger studies, however, need to be done in other tumor models, particularly those with lower immunogenicity than 9L, to conclusively demonstrate the efficacy of this approach. Additionally, further work is needed to compare the effects of GM-CSF with other cytokines. Systematic histologic examination of brains of treated animals will also be important to confirm that no detrimental autoimmune effects are produced.

References: Dranoff G, Jaffee E, et al: Vaccination with irradiated tumor cells engineered to secrete murine granulocyte-macrophage colony stimulating factor stimulates potent, specific, and long-lasting anti-tumor immunity. Proc. Natl. Acad. Sci. USA 90: 3539-3543, 1993.

Tada M, deTribolet N: Recent advances in immunobiology of brain tumors. J Neurooncol 17:261-271, 1993.

Steinman RM: The dendritic cell system and its role in immunogenicity. Annu Rev Immunol 9L271-296, 1991.

Select Review in Neuro-Oncology

<http://www.neurosurgery.org/tumor/selectreview/>

Volume: 1, Issue: 1

Title: Treatment of patients with primary glioblastoma multiforme with standard postoperative radiotherapy and radiosurgical boost: prognostic factors and long-term outcome

Review Type: Article

Category: Adult Neurosurgery

Journal: J Neurosurgery, Vol: 90, No. 1: pages 72-77, Jan 1999

Authors: Shrieve DC; Alexander E 3rd; Black PM; Wen PY; Fine HA; Kooy HM; Loeffler JS

Summary: This paper describes the results obtained by the Harvard radiosurgery group of their protocol utilizing radiosurgery as an adjunctive boost in the treatment of glioblastoma multiforme. This is an update of their initial paper reporting 23 patients published in JCO in 1992. The current report includes 78 patients accrued between 1988 and 1995 with a median follow up of 40.8 months. Patients were selected for treatment with an identifiable residuum of less than 4 cm and received a radiosurgery boost (median of 12 Gy to the 85% line) prior to external beam. Only twelve patients received chemotherapy. The overall survival was 19.9 months with a two year survival of 35.9%. These results are a marked improvement over what has previously been reported in the literature. Acute toxicity was minimal but one half of patients needed to undergo reoperation at a median of 7.9 months after radiosurgery. 50% of the time, the pathology revealed only radionecrosis. The 1992 report of a survival advantage with radiosurgery boost was greeted with skepticism due to the small number of patients and likelihood of marked selection bias. The current results however confirm the earlier work in a much larger number of patients followed for an extended period of time. In addition, a RTOG recursive partitioning analysis by Curran et al. statistically defined classes of high grade glioma patients with a similar prognosis and thus allows us to compare apples to apples. Classwise comparisons reveal dramatic differences. For instance, among GBM patients less than fifty with a Karnofsky's performance status > 90% (RTOG Class III), the radiosurgery group obtained a survival of 29.5 months versus the RTOG experience of 17.9 months with standard external irradiation. Even the RTOG Class IV patients with age >50 and a performance status less than 70 or unable to work obtained a survival advantage of 18.2 months versus 8.9 months. This study is still subject to the criticism that undefined selection factors such as less residual tumor could account for the unusually good results. Until RTOG 93-05 is reported next year, this paper does provide a strong rationale for offering GBM patients with a discrete residuum the option of a radiosurgical boost. The major downside is the increased likelihood of reoperation for radionecrosis.

Select Review in Neuro-Oncology

<http://www.neurosurgery.org/tumor/selectreview/>

Volume: 1, Issue: 1

Title: Transsphenoidal Microsurgical Therapy of Prolactinomas: Initial Outcomes and Long-term Results

Review Type: Article

Category: Adult Neurosurgery

Journal: Neurosurgery, Vol: 44, No. 2: pages 254-263, Feb. 1999

Authors: Tyrell, J.B, Lamborn, K.R., et al.

Summary: The authors review the outcomes of 219 women treated surgically for prolactinomas by one neurosurgeon during the periods 1976 to 1979 and 1988 to 1992. They report a clinical remission rate of 97% after a median follow-up period of 3.2 years and 84% after a median follow-up period of 15.6 years. Prolactin levels 200ng/ml and higher, invasive adenomas led to poorer outcomes (37-41% remission). Lower postoperative prolactin levels were most predictive of long-term remission. Morbidity in this series consisted of nine complications in six patients without permanent sequelae. There were no mortalities. These results compare favorably with those attained by medical management without the need for life long therapy.

Reviewers of this article commented on the low morbidity associated with medical management but acknowledged that if equally low surgical morbidity could be expected (as was achieved by the surgical team in this report), surgical intervention in young women with Grade I or II microadenomas could be considered as primary therapy.

Select Review in Neuro-Oncology

<http://www.neurosurgery.org/tumor/selectreview/>

Volume: 1, Issue: 1

Title: Intra-arterial Cereport (RMP-7) and Carboplatin: A Dose Escalation Study for Recurrent Malignant Gliomas

Review Type: Article

Category: Adult Neurosurgery

Journal: Neurosurgery, Vol: 44, No. 2: pages 270-279, Feb. 1999

Authors: Cloughesy, T., Black, K., et al.

Summary: Various attempts have been made to improve drug delivery to brain tumors in the hope of improving response rates. The authors of this paper describe a Phase I study employing intra-arterial carboplatin preceded by an escalating dose of the bradykinin analog RMP-7 to treat recurrent malignant gliomas. RMP-7 has been shown to transiently disrupt the blood-brain-tumor barrier and 10 to 300 ng/kg were administered intra-arterially followed by 100 mg of intra-arterial carboplatin. The authors found that in the 12 patients enrolled, weakness was the most prevalent adverse response occurring in 8 patients. Headache occurred in 6 patients. Seizures, sensory loss, and cortical blindness in 2 each and a third nerve palsy in one. No Grade IV toxicities were observed and thus the maximum tolerated dose was not established. Karnofsky score was not adversely affected overall for those patients who had tumor response. Tumor "shrinkage" was observed in three of six evaluable patients who received a dose of 300ng/kg. Reviewers of the article expressed concern about the potential neurotoxicity associated with this therapy, particularly given the fact that treatment remains palliative for most recurrent glioma patients. All stressed the need for further studies to better define the efficacy and potential toxicity of this treatment strategy. Other approaches for improving drug delivery were mentioned including osmotic blood-brain barrier disruption, polymer based local delivery systems and interstitial delivery using convection bulk flow techniques.

Select Review in Neuro-Oncology

<http://www.neurosurgery.org/tumor/selectreview/>

Volume: 1, Issue: 1

Title: Malignant transformation of p53-deficient astrocytes is modulated by environmental cues in vitro.

Review Type: Article

Category: Basic Science

Journal: Cell Growth & Differentiation, Vol: 10, No. 2: pages 73-86, February 1999

Authors: Bogler O, Nagane M, Gillis J, Huang H-J Su, and Cavenee WK.

Summary: How significant is the loss of p53 to gliomagenesis? Lost expression of the tumor suppressor gene, p53, is considered an early event in the tumor transformation of astrocytes, but the sufficiency or adequacy of this single genetic aberration to drive tumor progression remains unclear. The investigators developed a purified population of murine astrocytes homozygous for p53 loss to explore whether propagation of these cells under different growth conditions would lead to a tumorigenic phenotype of the astrocytes. From this focused and direct study, it becomes clear that loss of p53 is inadequate in itself to drive malignant transformation of astrocytes. Genetic events driven by chronic stimulation with either EGF or factors contained in fetal calf serum are necessary for subsequent genetic reprogramming of p53 deficient astrocytes to adopt tumorigenic behavior. Sustained growth of the astrocytes using bFGF did not lead to a malignant transformation. The DISCUSSION section of this manuscript is highly valuable reading for gaining perspective on the challenges of assigning biochemical cascades or genetic sequences of events that mature into malignant transformation of astrocytes. The often unspoken hope of molecular genetics is to map out the course of events that lead to the malignant phenotype. This paper is an outstanding description of the complexity of realizing that hope, and offers documentation for the likely prospect that there is more than one pathway leading to neoplasia.

Select Review in Neuro-Oncology

<http://www.neurosurgery.org/tumor/selectreview/>

Volume: 1, Issue: 1

Title: Differential Expression of MMAC/PTEN in Glioblastoma Multiforme: Relationship to Localization and Prognosis.

Review Type: Article

Category: Basic Science

Journal: Cancer Research, Vol: 59, No. 8: pages 1820-1824, April, 1999

Authors: Sano T, Lin H, Chen, X, Langford, LA, Koul D, Bondy ML, Hess Kr, Myers JN, Hong Y-K, Yung WKA, Steck PA.

Summary: The tumor suppressor gene MACC/PTEN on chromosome 10 encodes a phosphatidylinositol triphosphate phosphatase that modulates cell growth and apoptosis. In glioblastoma (GBM), loss of heterozygosity (LOH) affecting the MACC/PTEN locus has been reported in 75-95% of the tumors. In comparison, somatic mutations only occur in 10-35% of GBMs, suggesting other oncogenic mechanisms. In this report, the authors examined the levels of MACC/PTEN transcript in 42 lower grade gliomas and 78 GBMs to determine whether altered expression of the normal gene also contributed to the oncogenesis of GBM. Using semi-quantitative RT-PCR, the relative expression of MACC/PTEN was found to be highest in normal brain tissue, less in 40% of the lower grade tumors and lowest in 80% of the GBMs. A good correlation was observed using immunohistochemical analyses. About 70% of the GBMs and 25% of the lower grade tumors lacked protein. However, a population of those tumors expressing high levels of protein had two populations of cells, MACC/PTEN-positive and MACC/PTEN-negative tumor cells. Kaplan-Meier survival plots showed a significantly better prognosis for patients with tumors expressing high levels of MACC/PTEN, regardless of tumor grade. The authors conclude that additional mechanisms other than gene deletion and/or mutation may downregulate MACC/PTEN expression and thereby contribute to oncogenesis. In addition, the loss of expression is prognostic of poor patient outcome. Thus, the MACC/PTEN staining pattern may be a useful tool to identify not only those patients having complete loss, but also those patients having tumors with mixed populations who are presumably at a greater risk.

Select Review in Neuro-Oncology

<http://www.neurosurgery.org/tumor/selectreview/>

Volume: 1, Issue: 1

Title: SU5416 is a Potent and Selective Inhibitor of the Vascular Endothelial Growth Factor Receptor (Flk-1/KDR) that Inhibits Tyrosine Kinase Catalysis, Tumor Vascularization, and Growth of Multiple Tumor Types.

Review Type: Article

Category: Basic Science

Journal: Cancer Research, Vol: 59, No. 1: pages 99-106, January, 1999

Authors: Fong TAT, Shawver LK, Sun L, Tang C, App H, Powell TJ, Kim YH, Schreck R, Wang X, Risau W, Ullrich A, Hirth KP, McMahon, G.

Summary: VEGF is a potent inducer of angiogenesis in many tumor types, including glioblastoma. The binding of VEGF to its receptors, Flk-1/KDR and Flt-1, results in signal transduction pathways that lead to the increased endothelial cell proliferation required for angiogenesis. Since Flk-1/KDR has been implicated in mitogenesis of endothelial cells, the authors sought to develop a synthetic inhibitor that selectively targets the Flk-1/KDR receptor. In this report they characterized a novel compound SU5416. This compound inhibits tyrosine autophosphorylation on Flk-1/KDR thereby preventing the downstream signaling cascade normally induced by VEGF binding. When administered to Flk-1-transfected NIH3T3 cells in vitro, SU5416 inhibited receptor phosphorylation in a dose-dependent manner and decreased BrdU incorporation. The selective activity of SU5416 on Flk-1/KDR was demonstrated by the complete lack of activity against EGFR- and insulin receptor-transfected NIH3T3 cells and the greater than 20 fold reduced activity against PDGFR-transfected NIH3T3 cells. In vivo, SU5416 administration significantly inhibited the subcutaneous growth of 8 of 10 different tumor types tested, demonstrating a broad tumor efficacy. In addition, the efficacy was not dependent on site of tumor implant. SU5416 administration resulted in decreased C6 glioma tumor growth and vascularization; when implanted either subcutaneously or under the serosa of the colon. The authors suggest that SU5416 is a promising anti-angiogenic therapy with the potential for treating a number of cancers and their metastases.

Select Review in Neuro-Oncology

<http://www.neurosurgery.org/tumor/selectreview/>

Volume: 1, Issue: 1

Title: Phenotypic analysis of human glioma cells expressing the MMAC1 tumor suppressor phosphatase

Review Type: Article

Category: Basic Science

Journal: Oncogene, Vol: 18, No. : pages 1261-1266, Feb 1999

Authors: Morimoto, A.M. et al

Summary: MMAC1/PTEN/TEP1 is the tumor suppressor gene on chromosome 10 that is implicated in a variety of cancers. It is inactivated by classical tumor suppressor gene mechanisms, frequently suffering point mutations on one allele, followed by the loss of the remaining wild-type allele, a process that results in the loss of heterozygosity at that locus. MMAC1 encodes a dual specificity protein phosphatase, thought to be involved in attenuating intracellular signals transmitted by phosphorylation. Therefore, the loss of functional wild-type MMAC1 protein would remove an -off+ switch from several pathways (not all known at the present time), allowing excessive signal to contribute to tumorigenesis. One prediction of these findings is that reintroduction of MMAC1 into cancer cells lacking the gene would reduce the cells ability to form tumors. Morimoto et al show that when wild-type MMAC1 is introduced into U373 glioma cells, which express a truncated form of the protein, it causes a reduction in the growth rate of these cells and reduces the number of colonies that they form in soft-agarose. This is the expected behavior of a tumor suppressor gene, exemplified by the retinoblastoma gene, RB. However, unlike RB, which suffers missense mutations in only 20% of cases (favoring truncations that result in the absence of functional protein), MMAC1 often suffers missense mutations. Intriguing in this context is the authors' finding that a mutated, full length MMAC1 protein can actually contribute to the transformed phenotype of glioma cells, as measured by growth rate and anchorage independent colony formation. The observation that this effect occurs in cells lacking wild-type MMAC1 suggests that it is not a straightforward dominant negative mechanism. This then raises the possibility that mutant MMAC1, like its fellow tumor suppressor gene p53, may also have the gain of function attributes of an oncogene.

Select Review in Neuro-Oncology

<http://www.neurosurgery.org/tumor/selectreview/>

Volume: 1, Issue: 1

Title: C-Myc Oncogene Family Expression in Glioblastoma and Survival

Review Type: Article

Category: Basic Science

Journal: Surgical Neurology, Vol: 51, No. 5: pages 536-42, May 1999

Authors: Herms JW, et al.

Summary: The authors correlate the expression of myc proto-oncogenes (c-myc, N-myc and L-myc) and of the max (putative tumor suppressor) gene in GBMs from 46 patients and correlate expression and expression ratios to survival. They found no correlation between length of survival and expression of these genes in patients less than 60 years of age. In patients over 60 years of age at presentation, however, there was a direct correlation between length of survival and the ratio of max to myc expression.

Select Review in Neuro-Oncology

<http://www.neurosurgery.org/tumor/selectreview/>

Volume: 1, Issue: 1

Title: Oncolytic virus therapy of multiple tumors in the brain requires suppression of innate and elicited antiviral responses.

Review Type: Article

Category: Basic Science

Journal: Nature Medicine, Vol: 5, No. 8: pages 881-887, Aug 99

Authors: Ikeda et al

Summary: The treatment of multiple tumors in the brain remains palliative, at best. Viruses have been modified genetically so that they can replicate in and lyse tumor cells in a selective manner. To administer these viruses to multiple tumors in the brain, arterial injection techniques have been proposed. In this report, however, the authors found that blood/plasma from animals and humans rapidly inactivates the tumor-selective (oncolytic) virus. In-vitro experiments reveal that this inactivation is due at least partially to blood components that participate in the innate defense mechanisms of the host against pathogens. Specifically 2 components, complement and immunoglobulin M, appear to inactivate the virus, thereby limiting the anticancer effect. The authors go on to show that immunosuppressive agents (such as cyclophosphamide that limits IgM production), and complement inhibitors can reverse this effect. In fact, when the oncolytic virus is delivered intra-arterially in animals with 3 distinct brain tumors in combination with cyclophosphamide, infection of all tumor masses occurs, followed by significant involution and disappearance of the tumors. This study, therefore, indicates that oncolytic viral therapies for single or multiple tumors in the brain might be facilitated by limiting complement and or IgM action against the virus.

Select Review in Neuro-Oncology

<http://www.neurosurgery.org/tumor/selectreview/>

Volume: 1, Issue: 1

Title: SPARC: A Potential Diagnostic Marker of Invasive Meningiomas.

Review Type: Article

Category: Basic Science

Journal: Clinical Cancer Research, Vol: 5, No. 2: pages 237-241, Feb 1999

Authors: Rempel, SA., Ge, S and Gutierrez, JA

Summary: This paper describes the use of qualitative immunohistochemistry against SPARC (secreted protein acidic and rich in cysteine), also known as BM-40 and osteonectin. SPARC is a developmentally regulated gene that is expressed in a number of cell types. It is secreted into the extracellular matrix where it may modulate cell adhesion through a receptor mediated event that induces changes in cytoplasmic components associated with focal adhesions, or it may interact directly with extracellular matrix components such as Vitronectin to modulate cell adhesion. SPARC is also overexpressed in the highly infiltrative human astrocytic tumors.

The authors performed immunohistochemistry using an anti-SPARC antibody (Haematological Technologies, Inc., Essex Junction, VT) on formalin-fixed paraffin embedded sections. These sections were then scored for staining intensity. The authors found that SPARC was not expressed in nine benign, non-invasive meningiomas but was highly expressed in 20 invasive tumors regardless of the grade given to these tumors based on histological characteristics alone. The authors also found a few meningiomas with high SPARC expression for which there was no evidence for invasiveness on the initial resection; however, the aggressiveness of these tumors and evidence of invasiveness was identified when these tumors recurred.

Overall, this paper provides evidence that immunohistochemical evidence of SPARC expression may be a useful tool in predicting the recurrence and invasiveness of histologically benign meningiomas.

Select Review in Neuro-Oncology

<http://www.neurosurgery.org/tumor/selectreview/>

Volume: 1, Issue: 1

Title: Receptor for interleukin 13 is a marker and therapeutic target for human high-grade gliomas

Review Type: Article

Category: Basic Science

Journal: Clinical Cancer Research, Vol: 5, No. : pages 985-990, 1999

Authors: Debinski W, Gibo DM, Hulet SW, Connor JR, Gillespie GY

Summary: Interleukin 13, an immune regulatory cytokine secreted by activated T cells, acts on B cells, monocytes, macrophages and endothelial cells by binding to a heterodimeric receptor complex that it also shares with IL-4 (IL13/IL4R). IL13 and IL4 regulate immune responses similarly and the IL13R/IL4R complex is expressed not only on immune cells but also on some adenocarcinomas. In contrast, several previous reports from the Debinski group have established that human glioma cells in culture over-express a restrictive receptor for Interleukin-13 (IL13R) to which IL-4 cannot bind. Importantly, no glioma cell signaling function has been observed for the glioma-associated IL13R. Thus, the clinical relevance of expression of this unique IL13R by glioma cells is that genetically engineered fusion proteins combining IL-13 and the Pseudomonas exotoxin could be used to specifically target glioma cells. Since the majority of previous studies have involved cultured human glioma cell lines, it was important to demonstrate that this restrictive IL13R was also expressed by glioma cells in situ. This paper documents their observation that frozen sections from 23 of 25 surgical GBM specimens bound radiolabeled IL13 avidly and this binding was specific as shown by their capacity to block it with unlabeled IL13 but not with unlabeled IL4 or unlabeled transferrin. Importantly, normal brain tissue did not appear to bind radiolabeled IL13 specifically. Finally, they demonstrated the clinical potential for targeting this receptor with the IL13-PE fusion cytotoxin. Immunocompromised mice bearing established U373MG gliomas on their flanks or U251MG gliomas intracerebrally were effectively treated by intratumoral cytotoxin injection, as demonstrated by either tumor regression of the flank tumors or prolonged survival of mice with intracerebral gliomas. A recent review (Critic. Rev. Oncogen 9: 256-268, 1998) of this topic can provide more information.

References: Debinski, W., Obiri, N.I., Powers, S.K., Pastan, I., Puri, R.K. Human glioma cells overexpress receptor for IL13 and are extremely sensitive to a novel chimeric protein composed of IL13 and pseudomonas exotoxin. Clin. Cancer Res. 1: 1253-1258, 1995.

Debinski, W., Miner, R., Leland, P., Obiri N.I., Puri, R.K. Receptor for interleukin (IL) 13 does not interact with IL4 but receptor for IL4 interacts with IL13 on human glioma cells. J. Biol. Chem. 271: 22428-22433, 1996.

Debinski, W., Gibo, D.M., Obiri, N.I., Kealiher, A., Puri, R.K. Novel anti-brain tumor cytotoxins specific for cancer cells. Nature Biotechnol. 16: 449-453, 1998.

Debinski, W. An immune regulatory cytokine receptor and glioblastoma multiforme: an unexpected link. Critic. Rev. Oncogen. 9: 256-268, 1998.

Select Review in Neuro-Oncology

<http://www.neurosurgery.org/tumor/selectreview/>

Volume: 1, Issue: 1

Title: Pituitary Adenomas and Granular Cell Tumors: Incidence, Cell Type, and Location of Tumor in 100 Pituitary Glands at Autopsy

Review Type: Article

Category: Neuro-Pathology

Journal: Am J Clin Path, Vol: 111, No. 6: pages 817-825, June, 1999

Authors: Tomita, T, Gates, E.

Summary: One hundred autopsy pituitary glands were sectioned at 1.5 mm intervals revealing 26 incidental adenomas in 24 glands. Most of the adenomas were less than 3 mm in diameter, the largest measuring 6mm in diameter. Twenty-five of the adenomas were either non-functioning or lactotrophic. One adenoma was corticotrophic. In view of this high rate of incidental adenomas, clinical/pathologic correlation is sometimes required to determine whether adenomas found during surgery are clinically significant or incidental.

Select Review in Neuro-Oncology

<http://www.neurosurgery.org/tumor/selectreview/>

Volume: 1, Issue: 1

Title: Molecular Analysis of Microdissected de Novo Glioblastomas and Paired Astrocytic Tumors

Review Type: Article

Category: Neuro-Pathology

Journal: J. Neuropathol. Exp. Neurol., Vol: 58, No. 2: pages 120-128, Feb. 1999

Authors: Cheng Y, Ho-Keung N, Min D, et. al.

Summary: De novo glioblastomas, defined by a duration of symptoms less than 3 months, show a high rate of epidermal growth factor receptor (EGFR) amplifications. In contrast, secondary glioblastomas which progress over time from low grade astrocytomas are associated with a high rate of mutations in the p53 gene. After reviewing 178 astrocytomas, the authors identified 29 de novo glioblastomas associated with areas of low grade astrocytoma in the tissue blocks. Surprisingly, these de novo glioblastomas showed a high rate of p53 abnormalities(68%) with only 17% EGFR amplifications. Microdissected low grade areas from these glioblastomas, in contrast with low grade astrocytomas, showed a high rate of 10q deletions and other abnormalities which were also present in the high grade areas of these tumors. The authors speculate that they have identified a subset of glioblastomas showing rapid clonal progression from low to high grade.

Select Review in Neuro-Oncology

<http://www.neurosurgery.org/tumor/selectreview/>

Volume: 1, Issue: 1

Title: Cellular Proliferation in Pilocytic and Diffuse Astrocytomas

Review Type: Article

Category: Neuro-Pathology

Journal: J. Neuropath. Exp. Neurol., Vol: 58, No. 1: pages 46-53, Jan. 1999

Authors: Giannini C, Scheithauer B, Burger P, et. al.

Summary: This study presents MIB-1 (Ki-67) proliferative indices, mitotic rates, and survival data from 131 pilocytic astrocytomas and 140 diffuse astrocytomas. The major conclusions are: 1) Within the pilocytic category, MIB-1 indices were all less than 4% and could not be used to predict survival. 2) Within the grade 2 and 3 diffuse astrocytomas, MIB-1 indices were better predictors of survival than mitotic rates. Tumors in this category with a single mitosis (often used as a criteria to upgrade astrocytomas from grade 2 to 3) behaved more like grade 2 than 3 astrocytomas. These findings suggest that the cut off point between grade 2 and 3 tumors may not be optimal in the St. Anne-Mayo system and may need to be revised. 3) Low MIB-1 proliferative activity could be seen in grade 2,3 or 4 astrocytomas and, consequently, could not be used to rule out a high grade tumor. 4) High MIB-1 proliferative activity (greater than 8% in this study) was not seen in grade 2 astrocytomas. Consequently, a high MIB-1 index is useful in diagnosing high grade astrocytomas. 5) Readers are reminded that MIB-1 indices have not been standardized and while internally consistent, absolute values may vary considerably between different laboratories.

Select Review in Neuro-Oncology

<http://www.neurosurgery.org/tumor/selectreview/>

Volume: 1, Issue: 1

Title: Identification of subgroups of oligodendroglial tumors by comparative genomic hybridization

Review Type: Article

Category: Neuro-Pathology

Journal: J Neuropathol Exp Neurol, Vol: 58, No. 6: pages 606-612, June 1999

Authors: Jeuken JWM, Sprenger SHE, Wesseling P, et al

Summary: Comparative genomic hybridation was performed on 12 high grade oligodendroglial tumors (HGOT) and 17 low grade(LGOT), yielding 2 identified groups of HGOT. The OTs were classified independently by two neuropathologists using grading criteria stated in the article and included gliomas with "some" astrocytic features but excluded those with "prominent" astrocytic features. The LGOT all showed -1p and/or -19q (usually both), among other abnormalities. HGOT were of interest as they could be divided into two exclusive groups each comprising 50% of total: those with -1p and/or -19q, and those with +7/-10 abnormalities. Survival data for the HGOT were briefly presented, without data on post biopsy therapy. The +7/-10 group showed more variable survival, and 2 of 6 pts survived < 1 yr, 1 died at 2 yrs. All remaining pts, including all pts with -1p/-19q HGOT, were surviving at >2 yrs. Retrospective histologic review of the HGOTs did not reveal definitively differentiating features between the +7/-10 and -1p/-19q groups, but the +7/-10 group tended to show more necrosis and less prominent oligodendroglial phenotype. Other studies have found LOH 1p and LOH 1p/19q are associated with chemosensitivity and improved survival, and homozygous del CDKN2A (on 9p) with poor survival. The authors of this study noted 9p loss was more frequent in the +7/-10 group (3 of 6 tumors vs 1 of 6 in the -1p/-19q). It is of interest that the authors identified this molecular genetic subset of HGOT that might display more aggressive behavior, however, further analysis of therapy/chemotherapy response and longer followup is also needed. As mentioned in the article, one may also consider how to answer the question whether these +7/-10 gliomas are or should be viewed as a oligodendroglioma subset, or as potentially other glioma(s) with a component of oligodendroglial like morphology.

Select Review in Neuro-Oncology

<http://www.neurosurgery.org/tumor/selectreview/>

Volume: 1, Issue: 1

Title: Choroid plexus epithelium (normal and neoplastic) expresses synaptophysin. A potentially useful aid in differentiating carcinoma of the choroid plexus from metastatic papillary carcinomas.

Review Type: Article

Category: Neuro-Pathology

Journal: J Neuropath Exp Neurol, Vol: 58, No. 4: pages 398-401, April 1999

Authors: Kepes J, Collins J.

Summary: The authors report synaptophysin immunostaining of choroid plexus epithelium using routine methods and paraffin embedded tissues. Normal choroid plexus was tested with polyclonal and monoclonal antibodies, and a very small number of choroid plexus neoplasms (papillomas and carcinomas) were tested with polyclonal antibodies. All were immunostained. This unexpected finding may prove useful, in conjunction with other immunostains and morphologic findings, in the distinction of choroid plexus neoplasms from metastatic non-neuroendocrine papillary neoplasms. However, only a very small number of choroid plexus neoplasms was evaluated, and the rate of immunostaining of CP neoplasms cannot be reliably ascertained based on this study. As comment, the pattern of immunostaining illustrated appears strong, but (to me) a rather diffuse cytoplasmic pattern. A variety of staining patterns may be observed with this antibody, including granular/punctate immunoreactivity seen frequently in neuronal lesions. Because of potential nonspecific staining and cross reactivity (among other factors) the finding of immunoreactivity for an antigen demonstrated by immunohistologic techniques alone does not prove the presence of that antigen, and the basis for synaptophysin staining in choroid plexus is not yet elucidated.

Select Review in Neuro-Oncology

<http://www.neurosurgery.org/tumor/selectreview/>

Volume: 1, Issue: 1

Title: Early induction of angiogenetic signals in gliomas of GFAP-v-src transgenic mice

Review Type: Article

Category: Neuro-Pathology

Journal: American Journal of Pathology, Vol: 154, No. : pages 581-590, Feb 1999

Authors: Theurillat, JP, Hainfellner, J., Maddalena, A., Weissenberger, J., Aguzzi, A.

Summary: Angiogenesis is critical for the development of solid tumor growth. In human gliomas vascular proliferation is a significant prognostic indicator. VEGF is a key mediator of tumor-induced angiogenesis in vivo. Thus, the present study examines whether tumor progression triggers angiogenic factors including VEGF and the angiogenic receptors: flt-1, flk-1, tie-1 and tie-2. The authors study the expression patterns of these factors using astrocytomas of GFAP-v-src transgenic mice. The transgenic mice observe glioma progression patterns that follow observed human glioma progression patterns, which is further demonstrated in the present study. The angiogenic switch, the abrupt up-regulation of molecules capable of inducing abnormal vessel growth (VEGF, flt-1, flk-1, tie-1 and tie-2), was seen early in astrocytoma progression of the transgenic mice. This is similar to what has been described in human gliomas. Thus, the authors suggest that the GFAP-v-src transgenic mice may provide a useful model for the study of potential antiangiogenic therapy research.

Select Review in Neuro-Oncology

<http://www.neurosurgery.org/tumor/selectreview/>

Volume: 1, Issue: 1

Title: Extracellular matrix-induced cell migration from glioblastoma biopsy specimens in vitro.

Review Type: Article

Category: Neuro-Pathology

Journal: Acta Neuropathologica, Vol: 97, No. : pages 231-239, March 1999

Authors: Mahesparan, R., Tysnes, B.B., Read, T.-A., Enger, P.-O., Bjerkvig, R., Lund-Johansen, M.

Summary: The present study examines the interaction between the extracellular matrix (ECM) and glioma migration and invasion. The authors indicate that the majority of knowledge on this interaction is based on studies of permanent cell lines. The permanent cell lines, however, do not necessarily present an accurate representation of the situation of glioma cells in vivo. The authors use glioma cells, obtained directly from biopsy specimens, propagated as multicellular organotypic spheroids as a more accurate representation of the in vivo environment, to test the effect of ECM on invasion. The spheroids contain blood vessels, connective tissue elements, ECM components and macrophages. They also maintain the same DNA ploidy and underlying genetic instability as the original tumor. A cell migration assay was used to assess the impact of various ECM molecules (laminin, fibronectin, collagen type IV and vitronectin) on glioma migration. The results indicate a highly variable response between the different biopsied glioma cells and ECM components used. Glioma migration stimulated in response to ECM molecules appeared to be determined by the specific biopsy sample rather than by specific ECM components. These results are much more heterogeneous than those obtained from studies of permanent cell lines. The authors suggest that there may be some common receptors involved in glioma cell interaction with the different ECM molecules. Further studies are recommended. This study provides a new and important model for understanding the interaction between glioma cell migration and ECM components. A better understanding of the molecular mechanism in vivo can help lead to new therapeutic approaches.

Select Review in Neuro-Oncology

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Volume: 1, Issue: 1

Title: Intrasellar paraganglioma presenting as nonfunctioning pituitary adenoma.

Review Type: Article

Category: Neuro-Pathology

Journal: Archives of Pathology and Laboratory Medicine, Vol: 123, No. : pages 429-432, May 1999

Authors: Sambaziotis, D., Kontogeorgos, G., Kovacs, K., Horvath, E., Levedis, A.

Summary: The authors present a case report of a 54-year-old male diagnosed with intrasellar paraganglioma. The physical examination gave a diagnosis of bitemporal hemianopsia, after MRI a large sellar mass was believed to be a nonfunctioning pituitary adenoma, yet after removal and morphologic analysis the features were consistent with paraganglioma. Histologic, immunocytochemical and electron microscopic analyses were used to determine the final diagnosis. Paragangliomas are very rare neuroendocrine tumors of neural crest origin. The authors cite only 4 previously reported cases of paraganglioma arising in the pituitary fossa. As cited by the authors, paraganglion cells do not exist in the pituitary or adjacent structures. Thus, they suggest that in this case the tumor might have been derived from intrapituitary embryonic remnants of paraganglion cells. The paragangliomas of the sellar region are rare and morphologically difficult to diagnosis. This case is important in that it reveals some of the challenges faced by pathologists in diagnosing pituitary tumors of this type. This case suggests that paragangliomas should be included in the range of pituitary tumors considered in making diagnoses.

Select Review in Neuro-Oncology

<http://www.neurosurgery.org/tumor/selectreview/>

Volume: 1, Issue: 1

Title: Clinical Usefulness of T2-weighted FLAIR MRI of the CNS

Review Type: Article

Category: Neuro-Radiology

Journal: American Journal of Roentgenology, Vol: 172, No. 2: pages 529-536, Feb 1999

Authors: Adams JG, Melham ER

Summary: The authors review the benefits of the FLAIR [fluid attenuated inversion recovery] MR sequence in comparison to standard T1 and T2 sequences. The FLAIR sequence nulls signal from CSF therefore making other areas of signal abnormality (particularly cortical and periventricular lesions) more conspicuous on T2-weighted (FLAIR) scans. The authors review the advantages of using FLAIR when evaluating cystic brain masses including differentiating benign from malignant lesions. They also discuss the value of FLAIR MR for evaluating ischemic stroke, demyelinating disease, subarachnoid hemorrhage, trauma (DAI), and vascular malformations. Comment: FLAIR is a valuable sequence which only takes 4 minutes. Many MR centers have already replaced their proton-density scans with FLAIR scans.

Select Review in Neuro-Oncology

<http://www.neurosurgery.org/tumor/selectreview/>

Volume: 1, Issue: 1

Title: Intracranial germinomas: Correlation of imaging findings with tumor response to radiation therapy

Review Type: Article

Category: Neuro-Radiology

Journal: American Journal of Roentgenology, Vol: 172, No. 3: pages 713-716, Mar 1999

Authors: Moon WK, Chang KH et al

Summary: CT/MR images of 23 patients with pathologically proven pineal, suprasellar cistern or basal ganglia germinomas obtained before, during and after radiation therapy (RT) were retrospectively reviewed to assess response to RT based on presenting imaging characteristics. While all tumors demonstrated 85-100% response to RT at the completion of RT, those tumors with cystic portions present before initiation of treatment tended to respond more slowly to radiation therapy than those without cysts-i.e. residual cystic areas were often present at the conclusion of RT in lesions that presented with cystic areas while solid lesions more often were completely gone after completion of radiation therapy. However, residual cystic areas identified after completion of RT did eventually resolve within a year without the need for further radiation therapy.

Select Review in Neuro-Oncology

<http://www.neurosurgery.org/tumor/selectreview/>

Volume: 1, Issue: 1

Title: Cerebral gliomas and metastases: Assessment with contrast-enhanced fast fluid-attenuated inversion recovery MRI

Review Type: Article

Category: Neuro-Radiology

Journal: Radiology, Vol: 210, No. 2: pages 551-557, Feb 1999

Authors: Essig M, Knopp MV et al

Summary: The authors present data using a contrast-enhanced FLAIR sequence for delineation of primary and secondary brain neoplasms comparing it to standard FLAIR, T2-weighted and contrast-enhanced T1-weighted scans. The use of a contrast-enhanced FLAIR sequence reveals both T2 information (abnormal increasing signal reflects the extent of tumor spread and/or associated edema) and contrast-enhanced T1 information (extent of tumor neovascularity). The presented sequence may prove useful for radiation therapy planning or pre-operative planning purposes. However, the authors found that for delineation of metastases, their sequence was not as good as standard contrast-enhanced T1-weighted imaging. Comment: as current dedicated contrast-enhanced T1-weighted, FLAIR and T2 weighted sequences can be acquired in short periods of time (< 5 minutes each), it is hard to advocate switching to this new sequence as it does have some drawbacks.

Select Review in Neuro-Oncology

<http://www.neurosurgery.org/tumor/selectreview/>

Volume: 1, Issue: 1

Title: Suspected non-small cell lung cancer: Incidence of occult brain and skeletal metastases and effectiveness of imaging for detection -- Pilot study

Review Type: Article

Category: Neuro-Radiology

Journal: Radiology, Vol: 211, No. 1: pages 137-145, April 1999

Authors: Earnest F, Ryu JH et al

Summary: This paper looks at the incidence of brain and skeletal metastases from non-small cell lung cancer (NSCLC) patients with presumed operable disease, but staging greater than T1N0M0 (primary lung mass > 3 cm). This is important as current recommendations from the American Thoracic Society and European Respiratory Society state that no pre-operative imaging evaluation of the brain or skeleton is warranted in these patients unless clinical symptomatology suggests otherwise.

Eight of 29 patients had clinically occult brain (5 patients) or skeletal (5 patients) metastases.

By not including T1N0M0 patients in their study, the authors showed that a significant number of patients with presumed operable NSCLC harbor occult metastases that, if identified at the time of staging, might alter patient management. The authors used MR instead of CT as their gold standard for imaging and employed high doses of MR contrast for their imaging. In no cases did patients with initially negative head MR scans develop brain metastases on follow-up imaging within 1 year.

Comment: before operating on patients with NSCLC who have been staged to greater than T1N0M0, contrast-enhanced (preferably high dose) MR imaging of the brain should be performed regardless of presence or absence of clinical symptoms as the incidence of occult metastases is significant.

Select Review in Neuro-Oncology

<http://www.neurosurgery.org/tumor/selectreview/>

Volume: 1, Issue: 1

Title: Intraoperative MRI guidance for intracranial neurosurgery: Experience with the first 200 cases

Review Type: Article

Category: Neuro-Radiology

Journal: Radiology, Vol: 211, No. 2: pages 477-488, May 1999

Authors: Schwartz RB, Hsu L et al

Summary: The authors present their experience with intra-operative MR for intracranial neurosurgery in 200 cases. Surgery was performed in an MR-compatible operating room (OR) allowing essentially real-time evaluation of the intracranial compartment during neurosurgical procedures. Two intra-operative hemorrhages were identified at the time of surgery. Operation times and complication rates were similar to non-MR-guided procedures. The authors did not compare intra-operative MR to intra-operative ultrasound.

Comment: While it is clear that intra-operative MR would be extremely useful overcoming some of the negative aspects of standard frame-based or frameless stereotactic-guided procedures, the cost of converting an OR to MR compatibility (electronics, instruments, table, life support equipment, X-Ray equipment, citing an MR in an OR, etc), the inefficiency of such an MR scanner being used on only 1-2 patients/day, the cost of having a radiologist and MR technician on standby, etc. make intra-operative MR highly impractical. Intra-operative ultrasound utilizing a state-of-the-art unit (not the usual outdated machines that seem to be relegated to OR use) in the hands of a knowledgeable neurosonologist or neurosurgeon is essentially as good as MR and remains a much more practical way to employ real-time intra-operative imaging.

Select Review in Neuro-Oncology

<http://www.neurosurgery.org/tumor/selectreview/>

Volume: 1, Issue: 1

Title: Intracranial mass lesions: Sequential thallium and gallium scintigraphy in patients with AIDS

Review Type: Article

Category: Neuro-Radiology

Journal: Radiology, Vol: 211, No. 2: pages 507-512, May 1999

Authors: Lee VW, Antonacci V et al

Summary: The authors reviewed 21 HIV+ patients with intracranial masses evaluated with serial thallium and gallium studies. These patients had pathologically proven neoplastic (glioma, lymphoma) or non-neoplastic (infections, infarctions) processes. Positive thallium and gallium studies resulted in a sensitivity of 100% and a specificity of 80% for malignancy.

Comment: Currently the usual evaluation of an HIV+ patient with an intracranial mass is to treat presumptively for toxoplasmosis, re-image in 3-4 weeks and if no imaging response is seen, brain biopsy is considered or a lesion is simply treated with radiation for presumed lymphoma. This protocol is somewhat suboptimal as a) the risks of some anti-toxoplasmosis drugs are not benign, b) a diagnosis of lymphoma could be delayed for a month and c) it is expensive to hospitalize some of these patients for a month while making a diagnosis. If the high sensitivity/specificity observed in this study is confirmed in larger studies, such scintigraphic imaging may become routine -- particularly to rule out neoplasm in this patient population.

Select Review in Neuro-Oncology

<http://www.neurosurgery.org/tumor/selectreview/>

Volume: 1, Issue: 1

Title: Glial neoplasms: Dynamic contrast-enhanced T2*-weighted MRI

Review Type: Article

Category: Neuro-Radiology

Journal: Radiology, Vol: 211, No. 3: pages 791-798, June 1999

Authors: Knopp EA, Cha S et al

Summary: The authors utilized echo-planar perfusion MR imaging to assess the vascularity of glial neoplasms to attempt to improve targeting of tumor regions for biopsy and also to correlate with histologic grading.

There were statistically significant differences in vascularity (as determined by perfusion MR) of low-grade neoplasms in comparison to high grade neoplasms. As neovascularity (as determined histopathologically) is an important determinant of tumor grade, identifying the area of greatest neovascularity with imaging should identify the area of a tumor most likely to reveal the highest grade of malignancy at biopsy. The authors found that their perfusion MR technique was better than standard MR for identifying such areas of neovascularity. They currently routinely use it for both diagnostic and pre-biopsy evaluation of an intracranial mass.

Comment: This technique should be more sensitive than standard spin-echo contrast-enhanced T1-weighted MR for identifying areas of neovascularity. This is important for identifying areas of a tumor to biopsy and also to suggest that a possible sampling error has occurred if a lesion with neovascularity on perfusion MR demonstrates low grade histology on an initial biopsy. Once more widely available, perfusion MR could become the pre-biopsy MR imaging standard.

Select Review in Neuro-Oncology

<http://www.neurosurgery.org/tumor/selectreview/>

Volume: 1, Issue: 1

Title: MRI response of brain metastases after gamma knife stereotactic radiosurgery

Review Type: Article

Category: Neuro-Radiology

Journal: Radiology, Vol: 211, No. 3: pages 807-814, June 1999

Authors: Petersen AM, Meltzer CC et al

Summary: The pre-therapy and (at least one) post-therapy MR scans of 48 patients with intra-axial metastases treated with gamma knife radiotherapy were reviewed to determine the significance of the appearance of treated metastases on follow-up MR evaluation.

The authors found a correlation between the extent of response of a lesion to gamma knife therapy on the first post-treatment study and long term local lesion control. They found that lesions that had grown on the first post-treatment study tended to continue to grow on subsequent studies. However, a minority of lesions demonstrated some enlargement on the initial post-treatment study but demonstrated good response on subsequent studies suggesting a radiation effect and not progression of neoplasm was present on that initial post-treatment study.

Comment: For metastases treated with gamma knife therapy, the appearance of a treated metastasis on an initial post-RT MR scan correlates with longer term local control of that lesion. However, initial enlargement of a lesion on the first post-therapy scan does not always reflect failure to respond to the gamma therapy and further follow-up imaging is probably necessary to determine whether a lesion is truly growing or simply demonstrating transient radiation change.

Select Review in Neuro-Oncology

<http://www.neurosurgery.org/tumor/selectreview/>

Volume: 1, Issue: 1

Title: Use of Diffusion-Weighted MR Imaging in Differential Diagnosis between Intracerebral Necrotic Tumors and Cerebral Abscesses

Review Type: Article

Category: Neuro-Radiology

Journal: Am J Neurorad, Vol: 20, No. : pages 1252-1257, Aug 1999

Authors: Desprechins B, Stadnik T, et al

Summary: The differential diagnosis between intracerebral abscesses and cystic or necrotic tumors can be very difficult on conventional MR imaging. In this report, the authors compare the appearance of ten intracerebral necrotic tumors (eight gliomas, two metastases) with two cerebral abscesses on diffusion-weighted MR imaging (DWI). The abscesses demonstrated very high signal on DWI. This appearance was not seen in any of the cystic/necrotic neoplastic lesions.

Although only a small number of cases were examined, these findings suggest that DWI may offer another technique useful in the pre-operative differentiation of ring-enhancing intracerebral lesions. DWI should be used in conjunction with other techniques which also yield important clues in differentiating abscesses from tumors such as MR spectroscopy, MR perfusion studies, FLAIR imaging, and inspection of standard T1 and T2-weighted images.

Select Review in Neuro-Oncology

<http://www.neurosurgery.org/tumor/selectreview/>

Volume: 1, Issue: 1

Title: Paraneoplastic Syndromes

Review Type: Article

Category: Neurology

Journal: Archives of Neurology, Vol: 56, No. 4: pages 405-408, Apr. 1999

Authors: Dalmau JO, Posner JB

Summary: This review briefly but completely outlines the characterized antibodies, nervous system targets and clinical syndromes of the antineuronal paraneoplastic disorders. Special attention is paid to the molecular mechanisms of the Hu and Yo antigens and the Lambert-Eaton myasthenic syndrome. Anti-Yo antibodies are associated with gynecologic malignancies and the other two primarily with small cell lung carcinoma.

The authors state that recognition of these clinical syndromes can direct the search for a previously undiagnosed malignancy. This point is reinforced as the paraneoplastic syndromes typically present prior to discovery of the primary cancer and provide an opportunity for early intervention. For instance, they recommend hysterectomy and salpingoophorectomy for postmenopausal anti-Yo positive woman with normal mammograms even if pelvic imaging is normal. Treatment of those symptoms which respond to immunosuppression is briefly discussed.

Select Review in Neuro-Oncology

<http://www.neurosurgery.org/tumor/selectreview/>

Volume: 1, Issue: 1

Title: Alternative Therapy Use in Neurologic Diseases: Use in Brain Tumor Patients

Review Type: Article

Category: Neurology

Journal: Neurology, Vol: 52, No. 3: pages 617-622, Feb. 1999

Authors: Verhoef MJ, et al

Summary: The use of nontraditional medical therapies is increasing and many physicians are unaware of the extent of this practice in their patients. This study consisted of a prospective questionnaire designed to determine the prevalence of and patient reasons for using alternative medicines or therapies in the sole tertiary cancer care center in Southern Alberta. The cohort was followed an average of six months and included both malignant and benign intracranial neoplasms. Twenty four percent of patients received these therapies, most commonly consisting of herbs, mind-body therapies (e.g. faith healing, meditation) and shark cartilage. The most common reason given for taking these approaches was a perception that traditional medicine left the patient little hope and that they wanted to take a more active role in their treatment. Patient self assessment indicated that the majority (63%) of the therapies were perceived to be helpful in general but quality of life indexes built into the questionnaire showed no difference when compared to those patients receiving only traditional therapies. No adverse side effects were noted but the authors state that no tumor response was noted that was not explained by radio- or chemotherapy.

Select Review in Neuro-Oncology

<http://www.neurosurgery.org/tumor/selectreview/>

Volume: 1, Issue: 1

Title: Neurological Complications of Neurofibromatosis Type I in Adulthood

Review Type: Article

Category: Neurology

Journal: Brain, Vol: 122, No. 3: pages 473-481, March, 1999

Authors: Creange A., et al

Summary: Most previously reported series of NF-I patients have reported the neurologic manifestations of children. Younger patients present somewhat differently to the majority adult population described in this study. 158 NF-I patients (138 adults and 20 children) prospectively enrolled. Neurologic symptoms and findings were catalogued and followed for two years. A majority (55%) of the total group had one or more neurologic manifestations. Intrinsic brain neoplasms (e.g. optic pathway and brainstem glioma) and aqueductal stenosis were present in the adult population. However, these conditions all became symptomatic and required treatment exclusively when these patients were children. No adult developed progression of an intrinsic brain neoplasm during the follow up period. In contrast, adults complained primarily of pain and the only life threatening neurologic complications were malignant peripheral nerve sheath tumors. The authors recommend against serial neuroimaging in adults with optic pathway gliomas unless ophthalmologic testing changes. They stress a high suspicion of malignant transformation for neurofibromas that change rapidly in size or symptomatology.

Select Review in Neuro-Oncology

<http://www.neurosurgery.org/tumor/selectreview/>

Volume: 1, Issue: 1

Title: Medulloblastoma: Clinical and Biologic aspects

Review Type: Article

Category: Pediatrics/Pediatric Neuro-Oncology

Journal: Neuro-oncology, Vol: 1, No. 3: pages 232-250, July 1999

Authors: Packer RJ, Cogen P, Vezina G, & Rourke LB

Summary: In this updated, cogent review of medulloblastoma, the authors remind us that this tumor: 1] comprises ~20% of all pediatric (>18yo) CNS tumors; 2] has multiple histologic subtypes with an array of immunohistochemical & molecular genetic variations; and 3] presents in different patterns consequent to hydrocephalus, age, and dissemination via CSF pathways. Neuraxis MRI has become the diagnostic test of choice for pre-treatment determination of the extent of disease. Typically medulloblastomas present as well-defined, homogeneous, mid-line cerebellar vermian masses filling the fourth ventricle resulting in obstructive hydrocephalus. Contrast enhancement occurs in ~90%; and, ~20% display calcifications and/or cystic areas.

Standard surgical treatment consists of suboccipital craniotomy for microscopic excision of as much tumor as feasible while minimizing neurologic deficits resulting from deep cerebellar, brainstem, and cranial nerve manipulation. Ventricular shunts for CSF diversion are required in ~50% of cases despite aggressive tumor resection. Adjunctive treatment after surgery involves radiation and/or chemotherapy based on relapse risk assessment.

Assessment of risk remains somewhat arbitrary, but it is clear that extent of tumor resection, age, dissemination, and tumor biology identify populations with different prognoses. Patients above 3yo with near total excision of their undifferentiated tumor and no other disease are considered average risk cases. Other possible favorable prognostic factors include diploidy, high apoptotic index, and high expression of Trk C/Neurotrophin 3. Patients under 3yo and those with significant post-op residual disease, dissemination, or differentiated histologic patterns clearly do worse and are considered poor risk. Other unfavorable prognostic factors include brainstem involvement, aneuploidy, LOH 17q, c-myc amplification, or low apoptotic index. There may exist an intermediate risk group (not yet fully defined).

Currently, average risk cases receive post-op craniospinal axis radiotherapy (2400cGy) with local tumor boost (to 5400cGy) in conjunction with weekly vincristine followed by combination chemotherapy (CCNU, vincristine, and either cis-platinum or cyclophosphamide). Five year progression-free survival approaches 90% in this group. Poor risk patients above 3yo typically undergo radiotherapy as above plus boosts to disseminated tumor and more intense chemotherapy sometimes accompanied by stem-cell rescue or even pre-radiation multi-agent high dose chemotherapy. For children under 3yo, radiation is delayed because of known severe adverse consequences for the immature brain, hypothalamus, and spine. Current trials include high dose multi-agent chemotherapy with stem-cell rescue or bone marrow transplantation, intrathecal chemotherapy, or monoclonal antibodies; however, radiotherapy is often eventually required. Prognosis in poor risk cases currently approximates a 40% chance at 2 year progression-free survival.

Long term survivors of medulloblastoma treatment remain at significant risk of progressive cognitive decline, psychosocial difficulties, and endocrine deficits. These sequelae are partly linked to craniospinal radiation. The long term neurologic consequences of high dose chemotherapeutic strategies are not yet fully characterized. The goal of future protocols involves improving control of poor risk patients disease while minimizing cognitive, psychosocial, endocrine and neurologic impairments.

Select Review in Neuro-Oncology

<http://www.neurosurgery.org/tumor/selectreview/>

Volume: 1, Issue: 1

Title: Diffuse brain stem glioma: A review of stereotactic biopsies.

Review Type: Article

Category: Pediatrics/Pediatric Neuro-Oncology

Journal: Child's Nervous System, Vol: 15, No. : pages 235-238, March 1999

Authors: Cartmill M and Punt J

Summary: Cartmill and Punt review a series of 18 consecutive children presenting between 1990 and 1995 to the University of Nottingham medical center with symptoms and axial imaging findings suggestive of diffuse brainstem glioma (DBG). Each child underwent stereotactic, CT-guided biopsy under general anesthesia, using a supratentorial approach. Diagnostic tissue confirming glioma was obtained in all cases (8 grade IV, 5 grade III, 5 low grade). There were transient (< 7 days) new neurological deficits in 5 patients, but no lasting complications. All patients died of tumor progression within 48 months. The authors suggest that biopsy confirmation of DBG is safe and reliable in experienced hands. However, their study does not address the important issue of false positive diagnoses: that is patients who would have received inappropriate radiation therapy based on an incorrect clinical-radiographic diagnosis of DBG alone. Magnetic resonance spectroscopy has been particularly helpful as a confirmatory radiographic test in DBG, but was not reported in these patients. Post-mortem examination of patients radiated for a presumptive diagnosis of DBG will be critical to determine whether the (albeit low) risk and expense of stereotactic biopsy is justified.

Select Review in Neuro-Oncology

<http://www.neurosurgery.org/tumor/selectreview/>

Volume: 1, Issue: 1

Title: Gain of chromosome arm 17q and adverse outcome in patients with neuroblastoma.

Review Type: Article

Category: Pediatrics/Pediatric Neuro-Oncology

Journal: New England Journal of Medicine, Vol: 340, No. 25: pages 1954-1961, June 1999

Authors: N. Brown, S. Cotterill, M. Lastowska, S. O'Neill, A Pearson, D. Plantaz, M. Meddeb, G. Danglot, C. Brinkschmidt, H. Christiansen, G. Laureys and F. Speleman.

Summary: Brown et al. compiled a molecular genetic analysis of chromosome 17 in 313 primary neuroblastomas in patients from six European centers. A characteristic unbalanced gain of genetic material in the long arm of chromosome 17 was found in over half of the patients investigated. Gain of 17q was a significant predictor of adverse outcome and reduced five year survival rate (from 86 to 31 percent). In multivariate analysis, gain of 17q was predictive of outcome independent of traditional prognostic factors including age and anatomic tumor staging. Biologic markers including gain of 17q, deletion of 1p, and number of N-myc copies will serve to stratify children for appropriate therapy, including observation, intensive chemotherapy, surgery, radiotherapy and myeloablative therapy.

Select Review in Neuro-Oncology

<http://www.neurosurgery.org/tumor/selectreview/>

Volume: 1, Issue: 1

Title: Childhood medulloblastoma in Denmark, 1960-1984: A population based retrospective study.

Review Type: Article

Category: Pediatrics/Pediatric Neuro-Oncology

Journal: Child's Nervous System, Vol: 15, No. : pages 29-37, Jan. 1999

Authors: N. Agerlin, F. Gjerris, H. Brincker, J. Haase, H. Laursen, K. Moller, N. Ovesen, E. Reske-Nielsen and K. Schmidt.

Summary: Agerlin et al. Report their long-term (12 to 36 years) follow-up of 180 Danish children with histologically confirmed medulloblastoma of the posterior fossa. This represents all patients less than 15 years of age in Denmark receiving this diagnosis between 1960 and 1984. Their study includes both cases diagnosed at surgery (n=165) and at autopsy (n=15). They observed a male:female ratio of 2:1 and peaks of age distribution at approximately 3 and 7 years. Although the incidence of medulloblastoma in Denmark during this period was relatively stable, outcome from treatment changed dramatically, from 8% 5-year survival in 1960-4, to 36% 5-year survival in 1980-4. Total surgical resection and brain/tumor bed irradiation of greater than 40 Gy, with spinal irradiation of greater than 30 Gy, were associated with significantly higher survival rates. Chemotherapy was used in a minority of patients, and only in the latter twenty years of the study. Of 32 long-term survivors, 25 lived independently. Although suffering from the limitations of retrospective, population-based studies, Agerlin et al. provide valuable information about the incidence of this disease and its response to more aggressive, modern surgical and adjunctive therapy. Further data on this well-tracked population, including the outcome of additional chemotherapeutic interventions, will be welcome.

Select Review in Neuro-Oncology

<http://www.neurosurgery.org/tumor/selectreview/>

Volume: 1, Issue: 1

Title: Contamination of Poliovirus Vaccine with SV40 and the Incidence of Medulloblastoma

Review Type: Article

Category: Pediatrics/Pediatric Neuro-Oncology

Journal: Medical and Pediatric Oncology, Vol: 32: , No. 1: pages 77-78, January 1999

Authors: H.D. Strickler, P.S. Rosenberg, S.S. Devesa, J.F. Fraumeni Jr. and J.J. Godert

Summary: Simian virus 40 (SV40) has been shown to cause cancer in rodents and can immortalize human cells in vitro. Public health concerns have been heightened due to recent reports of the detection of SV40 DNA sequences in several tumors including osteogenic sarcomas, mesotheliomas as well as ependymomas and choroid plexus carcinomas. SV40 contaminated poliovirus vaccine was used throughout the USA during the late 1950s and 1960s. Strickler et al reviewed the cumulative US epidemiological data from the last 30 years and found no data to support excess risk of tumors related to SV40 exposure. A previous publication using data from the Connecticut tumor registry suggested that polio vaccine contaminated with SV40 was associated with an increased incidence of medulloblastoma in Connecticut. Strickler, in a concise and careful evaluation of the registry data, found no significant increased incidence during the 1950s when contaminated vaccine use occurred nor was there any change from baseline rates in the period immediately following vaccine induced exposure. This article provides important epidemiological data that can be helpful when discussing this topic with peers, patients and families.

Select Review in Neuro-Oncology

<http://www.neurosurgery.org/tumor/selectreview/>

Volume: 1, Issue: 1

Title: Clinical Features of Hypersensitivity Reactions to Carboplatin

Review Type: Article

Category: Pediatrics/Pediatric Neuro-Oncology

Journal: Journal of Clinical Oncology, Vol: 17, No. 4: pages 1141-1145, 1999

Authors: Markman M, Kennedy A, Webster P, Elson P, Peterson G, Kulp B, and Belinson J.

Summary: Markman et. al. review their experience with carboplatin hypersensitivity reactions in 205 patients with gynecological malignancies treated with multiple courses of carboplatin. Pediatric neuro-oncology has seen a dramatic increase in the use of carboplatin. This agent is very appealing compared to cisplatin because of its relative lack of nephrotoxicity and neurotoxicity as well as the relatively low associated incidence of severe emesis. Carboplatin has also become a main component for treating low-grade gliomas, in which it is used over a prolonged period of time. The authors note that the vast majority of carboplatin associated hypersensitivity reactions occur after a significant number of courses have been administered (median 8 courses, range 6-21). This observation is consistent with the establishment of hypersensitivity reactions among individuals working with platinum metals in industry.

The severity of the reactions varied, with several patients noting only itching or erythema (particularly palms and soles) or facial flushing. These minor symptoms were noted during the infusion, shortly after, or up to three days post treatment. Half of those patients exhibiting hypersensitivity reactions had a more severe reaction including diffuse erythroderma, tachycardia, wheezing, facial swelling, chills, rigors, throat and chest tightness, dyspnea, emesis hypertension or hypotension. One patient experienced a brief respiratory arrest. Only 38% of those with severe reactions developed initial symptoms within the first few minutes of infusion. The rest occurred after at least half of the infusion had occurred.

This paper adds to the literature of Carboplatin hypersensitivity reactions. Important information is provided regarding the character and time course of various reactions.

Select Review in Neuro-Oncology

<http://www.neurosurgery.org/tumor/selectreview/>

Volume: 1, Issue: 1

Title: Health Status in 52 Long Term survivors of Pediatric Brain Tumors

Review Type: Article

Category: Pediatrics/Pediatric Neuro-Oncology

Journal: Journal of Neuro-Oncology, Vol: 41, No. 1: pages 47-53, 1999

Authors: Nicholas K. Foreman, Paul M. Faestel¹, Joanne Pearson, Jennifer Disabato, Marty Poole¹, Greta Wilkening, Edward B. Arenson, Brian Greffe and Robert Thorne

Summary: Foreman et al studied health outcomes in 52 patients with primary intracranial tumors treated at Children's Hospital Denver. Patients were eligible if greater than 12 years of age and at least 5 years from diagnosis. A questionnaire based on the multi-attribute health status classification previously developed and reported by the group from McMaster University (senses, mobility, emotion, cognition, self-care) was modified to add questions concerning pain and cosmetic appearance. The questionnaire, which was administered over the phone, was answered by the patient's mother in every case. The mean age at diagnosis for this population was 8.1 years (1.1-15.3) and mean age at evaluation was 16.4 years (12.3-20.3). 77% received radiation. 70% received whole brain or craniospinal XRT. Mean age of patients receiving RT was 8.5 years (1.8-14.5) mean radiation dose was 52.3 Gy (44-60). The study group consisted of 24 patients with supratentorial and 28 with infratentorial tumors. Only one patient received chemotherapy alone.

Fifteen percent of the patients were blind, deaf or mute. 38% required educational assistance. 17% had limited social activities with 10% having no activities outside the household. Overall 87% of the respondents had deficits in multiple attributes. Foreman et al analyzed the data with regards to age at diagnosis, site, RT, chemotherapy, surgical resection and age at diagnosis. No significant differences could be found, though a trend for more significant disabilities was observed in patients with supratentorial lesions.

This study was conducted with a parent over the phone and did not include the patients' self assessments, furthermore the patient population is too small to look at craniopharyngioma versus medulloblastoma etc.

This paper reiterates that significant long term morbidity is found among long term survivors of pediatric brain tumors. Although patient self assessments were not included in this study, this paper provides a usable tool that may be incorporated in future studies to assess long term sequelae of tumor therapies in children.

Select Review in Neuro-Oncology

<http://www.neurosurgery.org/tumor/selectreview/>

Volume: 1, Issue: 1

Title: Identification of Prognostic Factors in Patients with Brain Metastases: A review of 1292 Patients

Review Type: Article

Category: Radiation Oncology

Journal: IJROBP, Vol: 43, No. 4: pages 795-803, Mar 1999

Authors: Lagerwaard FJ, Lenedag PC et al

Summary: A retrospective review of 1292 patients evaluated for brain metastases in the CT era. Interesting points are: only 22% had imaging follow-up, only 7% were managed with resection and RT. Analysis showed better ECOG PS (0-1), absent systemic disease, and response to steroids as well as age <70 were best predictors for better overall survival, but additionally, the use of radiotherapy (or S+RT) and initial response to steroid treatment and 1-2 lesions did better with regards to survival. This was a valiant attempt to use a large data base and extract some relevant data. The reader is particularly referred to Figure 2 to provide median survival data which is quite poor without treatment (admittedly selection bias may account for much of that).

Select Review in Neuro-Oncology

<http://www.neurosurgery.org/tumor/selectreview/>

Volume: 1, Issue: 1

Title: There is No Role for Hyperfractionated Radiotherapy in the Management of Children with Newly Diagnosed Diffuse Intrinsic Brainstem Tumors: Results of a Pediatric Oncology Group Phase III Trial Comparing Conventional vs. Hyperfractionated Radiotherapy

Review Type: Article

Category: Radiation Oncology

Journal: Int. Jounal Radiation Biol. Phys., Vol: 43, No. 5: pages 959-964, 1999

Authors: Mandell, L.R., Kadota, R., Freeman, C. et al.

Summary: This is a full report of the POG (Pediatric Oncology Group) trial which was presented in preliminary form at the 1997 ASTRO meeting. It is an important publication of the results of a straightforward phase III trial that has answered the question of whether hyperfractionated radiation is superior to conventional radiation for children with diffuse intrinsic brainstem gliomas. Throughout the 1980+s and early 1990+s, multiple phase II trials were conducted in children with diffuse infiltrating pontine gliomas utilizing hyperfractionation in the hope that escalating the total radiation dose would lead to improved tumor control and longer survival in these children who have a very poor prognosis. Hyperfractionation was a way of giving smaller doses of radiation more than once a day to a higher total dose in a way that would take advantage of the biologic differences between tumor and normal tissue. Between 1992 and 1996, POG enrolled 132 patients with brainstem gliomas (diagnosed on the basis of the usual clinical and MRI criteria) on a phase III trial comparing conventional RT (54Gy at 180cGy/fraction given once daily) to hyperfractionated RT (70.2Gy at 117cGy given twice daily). All patients also received cisplatin chemotherapy. The arms were well balanced, although it is somewhat surprising that on the hyperfractionated arm there were three children with a histologic diagnosis of oligodendroglioma, ganglioglioma and hemangioblastoma respectively. 108 of 132 patients had f/u MRIs that were centrally reviewed: there was an approximately 30% partial response rate in each arm; only one child in each arm achieved a radiographic complete response. Median time to disease progression was 6 and 5 months respectively; median time to death was 8.5 and 8 months respectively for the two arms. The authors, I think appropriately, conclude that for now, conventional once-daily RT is the appropriate mode of delivery of radiation in this patient population. It would be hard to justify the inconvenience to the patient and family, as well as the possibility of twice daily sedation in younger patients, of hyperfractionation given the results of this phase III trial. However, as so aptly pointed out in the accompanying editorial by Fisher and Donaldson, this is not to say that we should just continue to deliver conventional RT to this group of children who have a very poor prognosis. Clearly, innovative strategies need to be pursued to improve their outcome.

Select Review in Neuro-Oncology

<http://www.neurosurgery.org/tumor/selectreview/>

Volume: 1, Issue: 1

Title: Proton radiation therapy for chordomas and chondrosarcomas of the skull base.

Review Type: Article

Category: Radiation Oncology

Journal: J Neurosurgery, Vol: 91, No. 3: pages 432-439, Sep 1999

Authors: Hug EB; Loredano LN; Slater JD; DeVries A; Grove RI; Schaefer RA; Rosenberg AE; Slater JM

Summary: This paper details the results obtained at the Loma Linda University Proton Facility in the treatment of 58 patients with skull base chordomas and chondrosarcomas. These skull base tumors confront the radiation oncologist with often bulky residual disease adjacent to radiosensitive structures such as the brainstem and optic chiasm. Results with conventional fractionated irradiation have been dismal with suggested 5 year actuarial local control in the 20 to 30% range. A seminal series of papers from the Massachusetts General Hospital (MGH) Proton Facility established proton irradiation as the treatment of choice for skull base chordomas due to very high local control rates with relatively low brainstem toxicity. Munzenrider et. al. reported 5 year actuarial local control results of 95% for chondrosarcomas and 62% for chordomas. Proton irradiation allows a very high degree of dose conformality due to the physical dose distribution of the Bragg peak. This peak allows a higher ratio of dose to the prescribed target than to the surrounding normal brain tissue. The Loma Linda data confirm the MGH experience. After a mean follow up of 33 months, the local control rate with protons was 92% for chondrosarcomas and 76% for chordomas. Actuarial local control at 5 years was 75% and 59% respectively. Only 5% of patients developed grade 3/4 neurotoxicity. One patient developed bilateral blindness thought to be secondary to tumor progression.

These results confirm the vital role of high dose radiation treatment even in the setting of bulky residual disease. It should offer neurosurgeons the confidence to avoid potentially debilitating reoperations. What is unclear is whether this extraordinarily expensive technology offers any real benefits over stereotactic radiosurgery which is far less costly and widely available in the United States. Stereotactic radiosurgery allows sophisticated users to develop treatment plans which nearly mimic the dose conformality of proton beam plans. Preliminary gamma knife results from Pittsburgh and Mayo Clinic suggest moderately good local control with single fraction treatment in small numbers of patients. More likely to be successful is the advent of fractionated stereotactic radiation therapy or radiosurgery to gross disease used as a boost to conventional fractionation. Until such data is available, the Loma Linda results are outstanding and justify referral to a proton facility for these rare tumors.

Select Review in Neuro-Oncology

<http://www.neurosurgery.org/tumor/selectreview/>

Volume: 1, Issue: 1

Title: The effects of sequential versus concurrent chemotherapy and radiotherapy on survival and toxicity in patients with newly diagnosed high-grade astrocytoma

Review Type: Article

Category: Radiation Oncology

Journal: International J Radiation Oncology, Biology, and Physics, Vol: 44, No. 3: pages 535-543, June 1999

Authors: Kleinberg L; Grossman SA; Piantadosi S; Zeltzman M; Wharam M

Summary: Editor's note: two reviews were submitted for this paper. Both are listed below.

#1: The timing of chemotherapy in relation to radiation therapy for high grade gliomas has been an unanswered question. From 1988 to 1996 Johns Hopkins Oncology Center accrued 101 patients to two consecutive Phase II protocols testing cisplatin and BCNU as adjunctive treatment to radiation. The first protocol tested 3 months of neoadjuvant Cisplatin and BCNU given at 120 mg I.V. over 72 hours for three monthly cycles prior to XRT. Based on a promising response rate of 42%, the second protocol delivered the same chemotherapy concurrently with the start of cranial XRT. The overall survival was 12.8 months in the concurrent arm and 13.8 months in the sequential arm. The incidence of grade 3/4 leukopenia was 77% versus 40% and grade 3/4 thrombocytopenia was 89% versus 68% in the concurrent and sequential arms, respectively. There was no difference in anemia. There was no difference in the clinical risk of infection or bleeding. An elegant blood flow model in the paper concludes that concurrent chemoradiation results in hematopoietic toxicity due to effects on the circulating stem cells. The sequential protocol is currently being tested in a Phase III ECOG/SWOG trial.

One problem with the study is that different radiation regimens were employed in the two protocols. The sequential protocol delivered 51 Gray (5100 rads) over 17 fractions with a two week break after the first 30 Gy. Today, this is considered biologically inappropriate treatment due to accelerated tumor repopulation that occurs during a planned break. Most patients on the concurrent protocol were treated with continuous radiation therapy to dose of about 60 Gy which is currently the U.S. standard. This alone would tend to favor the concurrent protocol arm when in fact there was no survival difference. This paper confirms that cisplatin and BCNU are ineffective radiosensitizers for high grade astrocytomas and should not be given concurrently with XRT. Concurrent administration results in moderate hematopoietic toxicity due to the effects on circulating stem cells; this insight may lead to ways to sequence radiation and chemotherapy in order to minimize this problem. The good survival obtained with pre-irradiation chemotherapy seems to suggest that this is a reasonable strategy as long as progression is detected early and radiation therapy instituted promptly.

#2: This paper evaluates the impact on survival and toxicity of concurrent vs sequential chemotherapy and radiation therapy for patients with newly diagnosed high-grade astrocytomas. This study is from John Hopkins Oncology Center and evaluates two consecutive phase II trials. In the first trial, patients were treated with three months of Cisplatin and BCNU followed by radiation therapy. The second trial used similar chemotherapy regimen with radiation therapy given concurrently. Treatment was completed on majority of patients. Survival was similar in both groups. The incidence of grade 3-4 leukopenia were significantly worse in the concurrently treated group. This group also required increased platelet transfusion. Based on the results, they do not recommend further testing of concurrent chemotherapy and radiation therapy using Cisplatin and BCNU.

Select Review in Neuro-Oncology

<http://www.neurosurgery.org/tumor/selectreview/>

Volume: 1, Issue: 1

Title: Tumor size predicts control of benign meningiomas treated with radiotherapy

Review Type: Article

Category: Radiation Oncology

Journal: Neurosurgery, Vol: 44, No. 6: pages 1194-2000, June 1999

Authors: Connell PP, MacDonald RL, Mansur DB, Nicholas MK, Mundt JA

Summary: This retrospective study evaluates the effect of post-operative residual tumor size on the outcomes of patients treated with adjuvant radiation therapy for benign meningiomas. Extent of resection (biopsy versus subtotal resection) is a probable predictor for progression, however, residual tumor volume has not been well analyzed because postoperative imaging is a recent standard. The long natural history of meningiomas has precluded the publication of series with sufficient follow up in the CT/MRI era. This paper reports on 54 meningioma patients who underwent incomplete resections at the University of Chicago between 1984 and 1995 and post operative residual sizes were obtainable. All patients were treated with partial brain irradiation to a median dose of 54 Gy. The median follow up time was 55 months. The only predictor of 5 year actuarial progression free survival was residual tumor size. Residuum size greater than 5 cm was associated with a 40% progression free survival versus 93% for residuum size less than 5 cm. Cause specific survival was 65% and 97% respectively. Histology, RT dose, tumor location, and most importantly, extent of resection, were not significant predictors of progression or survival on multivariate analysis.

The obvious shortcoming of the paper is that it is a retrospective study without any consistent follow up imaging. Some patients probably had radiologic evidence of progression but were scored as clinically stable (more likely patients with smaller residual tumors with a longer time lag to become symptomatic). Conversely, some patients may have been scored as clinically progressing who were experiencing late radiation complications. The various authorities who were asked to comment on the paper stressed these limitations and felt the conclusions were unjustified. However, due to the long natural history of meningiomas, we may wait a long time for the publication of imaging based prospective studies. This study supports what radiation oncologists feel is intuitively obvious. A cornerstone of radiation biology is the concept that tumor control is a function of administering a sufficient dose of radiation to eradicate the viable tumor clonogens, which in turn is a function of tumor volume. This concept has been demonstrated consistently in vitro and in vivo. Cause specific survival is a parameter that is less sensitive to follow-up biases than progression free survival. Ultimately, survival is important to a patient, not asymptomatic radiologic progression. Partial brain doses to 54 Gy would be unlikely to cause fatal radionecrosis so late radiation complications would unlikely to influence the clinical scoring of this parameter. The CSS was highly influenced by the postoperative residuum size but not by the extent of surgical resection. In large tumors, this study does provide a rationale for performing aggressive surgical debulking and suggests the need for dose escalation techniques such as conformal or stereotactic radiation therapy.

Select Review in Neuro-Oncology

<http://www.neurosurgery.org/tumor/selectreview/>

Volume: 1, Issue: 1

Title: Stereotactic radiosurgery plus whole brain radiotherapy versus whole brain radiotherapy alone for patients with multiple metastases: a Prospective randomized trial

Review Type: Meeting Abstract

Category: Adult Neurosurgery

Meeting: American Association of Neurological Surgeons, April 24-29, 1999

Summary: Kondziolka et al. presented the interim results of their prospective, randomized controlled trial (PRCT) comparing whole-brain radiotherapy (WBRT) alone to WBRT plus radiosurgery in patients with 2-4 brain metastases. This trial is important in proving the efficacy of stereotactic radiosurgical boost in patients with multiple metastases to the brain. It is one of the few PRCTs in the neurosurgical literature, as well.

These interim results led to a premature closing of the trial because of improved survival and neurologic function in the radiosurgery group. The results have now been published in the International Journal of Radiation Oncology, Biology, and Physics (IJROBP).

The admission criteria for this trial included 2-4 metastases, known primary tumor, and no tumor greater than 25 mm. diameter.

Important results are summarized as follows: 1) 8% local failure with radiosurgery +WBRT at 1 year vs. 100% with WBRT alone 2) survival advantage for WBRT+initial radiosurgery vs. WBRT+delayed radiosurgery vs. WBRT alone.

3) No effect of systemic disease extent on control of brain disease

Summary: WBRT + radiosurgery for 2-4 mets improves control of brain disease and lengthens survival when compared to WBRT alone.

Select Review in Neuro-Oncology

<http://www.neurosurgery.org/tumor/selectreview/>

Volume: 1, Issue: 1

Title: Craniotomy for tumor: Outcomes in high-volume versus low-volume hospitals

Review Type: Meeting Abstract

Category: Adult Neurosurgery

Meeting: American Association of Neurological Surgeons, 4/24-4/29, 1999

Summary: The expansion of managed care has led to a fierce debate on quality of care and responsiveness to patient concerns. In an effort to improve their image, HMOs have taken to rating themselves and their doctors. This has caused a proliferation of outcomes assessment in an effort to grade quality of care. Managed care companies have tried to show excellent care in the community hospitals that make up their networks. In retaliation, academic centers have published research demonstrating the best outcomes in high-volume centers and especially academic medical centers in comparison to community hospitals. This very important report by Brem et al. follows on recent reports demonstrating improved outcome in myocardial infarction in high-volume academic centers compared to non-academic low-volume centers. In this study, results were examined for craniotomy for tumor.

In this Maryland-based report, high-volume was considered more than 50 craniotomies for tumor per year. Results of the study showed a statistically lower mortality and length of stay in academic high-volume centers compared with low-volume centers. Despite an average almost 3 days greater length of stay, smaller hospitals were still cheaper than academic centers by an average \$2,400.

These data are at the crux of the health-care debate. Better results and lower morbidity are obtained at academic centers, but at slightly higher cost. In the current climate, where managed care companies are making the decisions, it is likely that the cost factor will be the most important.

Select Review in Neuro-Oncology

<http://www.neurosurgery.org/tumor/selectreview/>

Volume: 1, Issue: 1

Title: Correlation between radiation reponse and genetic aberrations in glioblastoma multiforme

Review Type: Meeting Abstract

Category: Adult Neurosurgery

Meeting: American Association of Neurological Surgeons, 4/24-29 1999

Summary: This interesting paper from Kunwar et al. is an attempt to identify genetic determinants of radiation resistance in glioblastoma multiforme (GBM). The authors took 58 patients with pre- and post- radiation therapy (XRT) scans and classified their tumors as radiation resistant or radiation sensitive based on imaging progression or death during XRT. These tumors were then analyzed for chromosomal abnormalities.

The most common abnormality in the radiation resistant tumors was a gain of a whole chromosome 7. This was statistically associated with radiation resistance. Among tumors with a gain of chromosome 7 and loss of 14q22-24, 89% were radiation resistant.

Based on their results, the authors identify chromosome 7, 9p23-24, 13q14, 14q22-24, and 18q22-23 as promising sites to find genes associated with radiation resistance in GBM.

In any chromosomal study on GBM, it is hard to prove any cause and effect. Have the authors merely identified aggressive tumors which are not only radiation resistant but also chemoresistant and rapidly progressive? Any study for GBM has to take into account the overwhelming influence of age and performance status on outcome. These affect response to radiation as well. Nevertheless, studies such as this are useful starting points for designing in vitro work to test the effect of specific genes on radiation resistance.

Select Review in Neuro-Oncology

<http://www.neurosurgery.org/tumor/selectreview/>

Volume: 1, Issue: 1

Title: Phase I/II Study of Carboplatin and Thalidomide in Recurrent Glioblastoma Multiforme

Review Type: Meeting Abstract

Category: Medical Oncology

Journal: Proceedings of the American Society of Clinical Oncology, Vol: 18, No. : pages 144a, 1999

Authors: Glass J, Gruber ML, Nirenberg A

Meeting: American Society of Clinical Oncology, May 15-18, 1999

Summary: A phase I/II trial of Carboplatin and thalidomide, a putative anti-angiogenesis agent, was performed in 71 patients with recurrent glioblastoma multiforme. Carboplatin was given at a dose calculated using an AUC of 8 while the maximum tolerated dose (MTD) of thalidomide was 300 mg/m² by mouth daily. At the MTD, 64 patients were assessable for toxicity and 46 were assessable for efficacy. Five patients treated at the MTD had partial responses, 28 remained stable and 13 progressed. The estimated median survival in this group of recurrent glioblastoma patients was 40 weeks while the median response duration was 24 weeks. Major non-hematologic toxicities attributable to the thalidomide included constipation and drowsiness.

Select Review in Neuro-Oncology

<http://www.neurosurgery.org/tumor/selectreview/>

Volume: 1, Issue: 1

Title: Randomized Trial of Temodal (TEM) vs. Procarbazine (PCB) in Glioblastoma Multiforme (GBM) at First Relapse

Review Type: Meeting Abstract

Category: Medical Oncology

Journal: Proceedings of the American Society of Clinical Oncology, Vol: 18, No. : pages 139a, May 1999

Authors: Yung A, Levin VA, Albright R, Olson J, Fredericks R, Fink K, Prados M, Brada M, Spence A, Brunner J, Yue N, Dugan MH, Zaknoen S

Meeting: American Society of Clinical Oncology, May 15-18, 1999

Summary: This randomized phase II trial compared the efficacy of temozolomide, an oral methylating agent recently approved for use in patients with recurrent anaplastic astrocytomas, with procarbazine in adults with glioblastoma multiforme at first relapse. Temozolomide was given at a dose of 150-200 mg/m²/d for five days (repeated every 28 days) and procarbazine was given at a dose of 125-150 mg/m²/d for 28 days (repeated every 56 days). Progression free survival at 6 months and 6 month overall survival was 21% and 60% in the 112 patients treated with temozolomide versus 8% and 44% for the 113 patients treated with procarbazine. Health related quality of life data also favored temozolomide therapy at months 3 and 6 following study entry.

Select Review in Neuro-Oncology

<http://www.neurosurgery.org/tumor/selectreview/>

Volume: 1, Issue: 1

Title: Oral Shark Cartilage in the Treatment of Patients with Advanced Primary Brain Tumors. A Phase II Pilot Study

Review Type: Meeting Abstract

Category: Medical Oncology

Journal: Proceedings of the American Society of Clinical Oncology, Vol: 18, No. : pages 144a, May 1999

Authors: Rosenbluth RJ, Jennis AA, Cantwell S, DeVries J

Meeting: American Society of Clinical Oncology, May 15-18, 1999

Summary: Anecdotal data suggests that shark cartilage, a popularly used alternative medicine, has anti-cancer activity and may have anti-angiogenic properties. 12 patients with progressive primary brain tumors (10 glioblastomas) with a Karnofsky performance score of at least 50 were treated with 96 g/day of shark cartilage in 4 divided daily doses. Ten patients were evaluable. One patient had clinical progression at 11 weeks, 2 had stable disease at 20 and 24+ weeks, and 7 progressed after a minimum of 8 weeks of therapy. At the tested dose and schedule, shark cartilage had no activity against recurrent malignant brain tumors.

Select Review in Neuro-Oncology

<http://www.neurosurgery.org/tumor/selectreview/>

Volume: 1, Issue: 1

Title: Clinicopathologic Features Of Astroblastoma

Review Type: Meeting Abstract

Category: Neuro-Pathology

Meeting: American Association of Neuropathologists, June 17-20, 1999

Summary: We describe features of 17 astroblastomas in patients from 3- 45 years old (mean, 14 years) presenting with headaches or seizures. MRI showed well-circumscribed, contrast-enhancing, solid and cystic masses involving cerebral hemispheres(16 cases) or brain stem (1 case). All tumors had perivascular arrays of cuboidal or columnar epitheloid cells with broad processes. Typical were extensive perivascular hyalinization (94%), pushing borders (82%), degenerative necrosis (76%), and calcification (59%). Pseudopallisading necrosis (24%), infiltrative borders (18%), vascular proliferation (12%), multinucleated giant cells (18%), and macrophage clusters (18%) were less common. Mitoses (0-15/10 hpf) and MIB-1 labeling indices (1-18%) varied considerably. Tumor cells were reactive for S-100 and GFAP, and displayed focal membrane and cytoplasmic staining for EMA. Ultrastructurally, cytoplasm contained abundant intermediate filaments. No microvilli, cilia or desmosomes were noted. Cytogenetic study of one case showed alterations of chromosome 17p and 22q. Total resections were achieved in 13 of 15 cases for which follow-up was available. Of these 13, 10 received radiation therapy (mean dose, 5100 cGy). None of the totally resected tumors recurred (mean follow-up, 24-months). Only subtotal resections were possible in 2 cases. Both received radiation therapy (5320 and 7200 cGy). One tumor recurred after 8 months, causing death at 17 months; the other recurred after 37 months and the patient survives. Astroblastomas are discrete, solid and cystic gliomas occurring in the hemispheres of children and young adults. They have unique histopathologic profiles, but vary considerably in grade. Cures appear possible following total resection.

Select Review in Neuro-Oncology

<http://www.neurosurgery.org/tumor/selectreview/>

Volume: 1, Issue: 1

Title: Alterations Of Chromosome Arms 1p And 19q As Predictors Of Survival In Diffuse Gliomas

Review Type: Meeting Abstract

Category: Neuro-Pathology

Meeting: American Association of Neuropathologists, June 17-20, 1999

Summary: A recent report by Cairncross et al (JCN 90:1473, 1998) suggests that alterations of chromosome arms 1p and 19q are associated with chemotherapeutic response and overall survival in anaplastic oligodendrogliomas. We set out in the present study to further clarify the significance of these alterations in a broader set of tumors. FISH signals from DNA probes mapping to 1p and 19q common deletion regions were enumerated in 162 diffuse gliomas (79 astrocytomas, 52 oligodendrogliomas, and 31 mixed oligoastrocytomas). The oligodendroglial phenotype was highly associated with loss of 1p, loss of 19q, and combined loss of 1p and 19q. Survival analysis demonstrated that combined loss of 1p and 19q was statistically significant univariate and multivariate predictor of prolonged overall survival among patients with pure oligodendroglioma, including low grade examples. Furthermore, of the 14 oligodendroglioma patients with combined loss, none had died at time of last follow-up (67.5 mo. median follow-up). This favorable association of combined loss with survival was not evident in patients with astrocytomas or mixed oligoastrocytomas. Our study suggests that a combined histologic and genotype assessment could potentially improve existing strategies for patient stratification and management.

Select Review in Neuro-Oncology

<http://www.neurosurgery.org/tumor/selectreview/>

Volume: 1, Issue: 1

Title: Long Survivals And Therapeutic Responses In High-Grade Gliomas With Chromosome 1p Loss That Are Not Classic Anaplastic Oligodendrogliomas

Review Type: Meeting Abstract

Category: Neuro-Pathology

Meeting: American Association of Neuropathologists, June 17-20 1999

Summary: Allelic loss of chromosome 1p is a powerful predictor of chemosensitivity and long survival in patients with anaplastic oligodendrogliomas. Chromosome 1p loss also occurs in other subtypes of high-grade glioma, although far less commonly than in oligodendroglial tumors. We hypothesized that chromosome 1p loss might also offer prognostic information for patients with high-grade glioma other than classic anaplastic oligodendroglioma. We report five patients with high-grade gliomas that were diagnosed by neuropathologists as glioblastoma or anaplastic astrocytoma and that had remarkable neuroradiological responses to therapy or unexpectedly long survivals. All of the tumors from these five patients had chromosome 1p loss. We also assessed the frequency of chromosome 1p loss in a series of anonymous glioblastoma and anaplastic astrocytoma samples and demonstrate that this genetic change is uncommon, occurring in only 10% of cases. While any prognostic importance of chromosome 1p loss in high-grade gliomas other than classic anaplastic oligodendrogliomas can only be determined on larger and prospective series, the findings raise the possibility that some high-grade astrocytic and mixed gliomas with chromosome 1p loss may be especially sensitive to cytotoxic therapies and may follow different clinical courses.

Select Review in Neuro-Oncology

<http://www.neurosurgery.org/tumor/selectreview/>

Volume: 1, Issue: 1

Title: Molecular Genetic Analysis Of Oligodendroglial Tumors FOR Allelic Deletions On 1p And Mutations Of CDKN2C Gene At 1p32

Review Type: Meeting Abstract

Category: Neuro-Pathology

Meeting: American Association of Neuropathologists, June 17-20, 1999

Summary: Oligodendroglial tumors frequently show allelic losses on the short arm of chromosome 1. To narrow down the putative tumor suppressor gene site(s) on 1p, we have investigated 35 oligodendrogliomas and 10 oligoastrocytomas for loss of heterozygosity (LOH) at 21 highly polymorphic loci on chromosome 1 (19 loci on 1p and 2 loci on 1q). LOH at loci from 1p was found in 30 of the 45 tumors (67%). Two distinct putative tumor suppressor regions were identified: a distal region between D1S76 and D1S253 at 1p36.3, and a proximal region between D1S482 and D1S2743 at 1p34-p35. We also analyzed our tumor series for genetic alterations and expression of the cyclin dependent kinase inhibitor gene CDKN2C (p18INK4C) from 1p32. We found one recurrent anaplastic oligodendroglioma with a somatic CDKN2C mutation at codon 113 (GAA to TAA: Glu to Stop). The remaining 44 tumors of our series showed neither coding sequence mutations nor homozygous deletions of CDKN2C. Investigation of 35 tumors by differential reverse transcription-PCR revealed expression of CDKN2C transcripts in all instances. Our data thus provide first evidence for more than a single oligodendroglioma-associated tumor suppressor gene on 1p and implicate CDKN2C as a candidate tumor suppressor gene altered in a low fraction of oligodendroglial tumors.

Select Review in Neuro-Oncology

<http://www.neurosurgery.org/tumor/selectreview/>

Volume: 1, Issue: 1

Title: Quantitative Estimation of Microvascular Permeability with Dynamic Contrast-Enhanced MR Imaging: Correlation with Pathohistologic Grading

Review Type: Meeting Abstract

Category: Neuro-Radiology

Meeting: American Society of Neuroradiology, May 23-28, 1999

Summary: **PURPOSE:** The aim of this study was to assess whether dynamic contrast-enhanced MR imaging may be used to quantify blood volume and microvascular permeability in patients with brain tumors and whether these quantifications correlate with histologic grade of the tumor.

MATERIALS & METHODS: Ten consecutive patients with a spectrum of brain tumors underwent MR imaging; surgery followed within 1 week. The MR scan consisted of one pre- and six dynamic postcontrast 3D-SPGR data sets following bolus injection of single dose Gd-DTPA (TR/TE 8.3/1.5 msec, flip angle 30°, 1 nex, matrix 256x256, section thickness 3 mm, FOV 24 cm, acquisition time 32 s per volume of 28 slices). Signal intensity changes in blood and tissue were kinetically analyzed using a unidirectional two-compartment model which yields estimates of fractional tissue blood volume (BV[ml/cc]) and microvascular permeability, expressed as the transendothelial transfer constant kPS (ml/100cc*min).

RESULTS: Histologic analysis after surgical tumor resection revealed a spectrum of brain tumors spanning the range from glioblastoma multiforme (grade 4) through (oligo-) astrocytoma (grade 2) to one hemangioblastoma. Blood volume was highest in the vascular area of the hemangioblastoma (102.8%), lowest in an astrocytoma (1.9%) and did not correlate with the grade of the tumor ($p > 0.05$). Microvascular permeability (kPS), however, varied from 0.1 to 1.8 in grade 2 tumors and between 2.6 and 6.9 in grade 4 tumors. The hemangioblastoma demonstrated a kPS of 3.2.

CONCLUSION: Dynamic contrast-enhanced MR imaging allows a non-invasive determination of the tumor fractional blood volume and microvascular permeability (kPS). kPS increases with tumor grade. Thus, this MR technique can quantitatively assess tumor malignancy and demonstrate the most malignant area before a surgical biopsy.

REFERENCES: 1. Shames DM, Kuwatsuru R, Vexler V, Muhler A, Brasch RC. Measurement of capillary permeability to macromolecules by dynamic magnetic resonance imaging: a quantitative noninvasive technique. *Magn Reson Med* 1993; (29):616-22
2. Ostrowitzki S, Fick J, Roberts TP, Wendland MF, Aldape KD, Mann JS, Israel MA, Brasch RC. Comparison of gadopentetate dimeglumine and albumin-(Gd-DTPA)₃₀ for microvessel characterization in an intracranial glioma model. *J Magn Reson Imaging* 1998:799-806

KEY WORDS: Microvascular permeability, grading, brain tumors, contrast-enhanced MR imaging.

Select Review in Neuro-Oncology

<http://www.neurosurgery.org/tumor/selectreview/>

Volume: 1, Issue: 1

Title: In Vivo Differentiation of Tumor Recurrence vs Radiation Change: High Correlation Between Proton MR Spectroscopy and Neuropathology

Review Type: Meeting Abstract

Category: Neuro-Radiology

Meeting: American Society of Neuroradiology, May 23-28, 1999

Summary: **PURPOSE:** To test the hypothesis that proton MR spectroscopy at 3 T has sufficient spatial resolution and chemical specificity to distinguish radiation changes from tumor recurrence in astrocytoma patients.

MATERIALS & METHODS: Ten subjects who had received radiation therapy for high-grade astrocytomas were included in the study. Conventional MR imaging with gadolinium showed at least one focus of enhancement consistent with radiation change or tumor recurrence. MR spectroscopy was obtained in the following manner: a 16 x 16 axial metabolite image was acquired on a 3-T GE Signa scanner using a PRESS sequence (TE/TR = 144/1500, voxel size = 1.56 cc) including the area to undergo biopsy. In vivo spectroscopy results in the 10 subjects (15 biopsy sites) were correlated with histopathology of biopsy samples obtained within 1 week of the MR spectroscopy exam.

RESULTS: With in vivo 3-T MR spectroscopy a Cho/Cre ratio greater than 3.2 was indicative of recurrent astrocytoma ($p < 0.0001$) while a ratio less than 1.8 was indicative of radiation change ($p < 0.0001$). Patients with Cho/Cre ratio between 1.8 and 3.2 had biopsies that correlated with a mixture of radiation change and tumor. The Cho/Cre ratio was elevated in all cases compared to normal brain. NAA was decreased in both tumor and radiation change.

CONCLUSION: In vivo MR spectroscopy at 3-T field strength can differentiate tumor recurrence from radiation change in astrocytoma patients. The volume of tissue examined using this method is larger than with single or multiple biopsy specimens allowing for a more complete evaluation of a region of abnormal gadolinium enhancement.

Select Review in Neuro-Oncology

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What's Hot in Neuro-Oncology

Volume: 1, Issue: 1

Title: Oligodendroglial tumors and genetic prediction of response to PCV chemotherapy

Category: Adult Neurosurgery

Contributor(s): Nicholas Avgeropoulos, M.D

Institution: WDMCI at Florida Hospital

Summary: Determining the appropriate antibiotic for use in treatment of a particular infection is many times based on the results of a sensitivity panel. Using a similar approach to determine the chemosensitivity of a particular brain tumor is an analogously logical concept because as a whole, no clinical or histopathologic feature of brain tumors allows for an accurate prediction of response to chemotherapy. Unfortunately, other than oligo-containing gliomas, primary CNS lymphoma, and possibly primitive neuroectodermal tumors, primary brain tumors (mostly comprised of astrocytomas / glioblastomas) are also largely chemoresistant. Furthermore when chemosensitivity is demonstrated in vitro, these results do not necessarily translate directly to an in vivo response (pools of cellular mutants, various cytokines in the milieu, etc.) and as such, routine chemosensitivity testing is not utilized. Neuro-Oncology researchers have turned to molecular-cellular techniques to find a way to predict, facilitate, or otherwise exploit the process of tumor cell killing.

Louis, Cairncross, and colleagues have focused on the treatment of anaplastic oligodendroglioma (AO) with procarbazine, CCNU, and vincristine (PCV) where objective radiographic response rates are achieved in about two-thirds of patients. These investigators sought to correlate a unique constellation of molecular genetic alterations (loss of chromosomal arms 1p and 19q and gene deletions of CDKN2A [chromosome 9p]) with radiographic response and survival in a group of 39 AO patients where these clinical data had matured and were available [1]. They discovered that +allelic loss (or loss of heterozygosity) of chromosome 1p is a statistically significant predictor of chemosensitivity, and combined loss involving chromosomes 1p and 19q is statistically significantly associated with both chemosensitivity and longer recurrence-free survival after chemotherapy+. Additionally, +losses involving both chromosomes 1p and 19q were strongly associated with longer overall survival, whereas CDKN2A gene deletions and ring enhancement on neuroimaging were associated with a significantly worse prognosis+. Quite importantly, neither greater age at chemotherapy, lower KPS, nor the presence of necrosis on pathology was significantly associated with poor response to PCV.

These results suggest that molecular genetic analysis may aid therapeutic decisions and predict outcome in patients with anaplastic oligodendroglioma. Research efforts from other groups have largely confirmed and expanded the importance of these findings [2,3]. Although currently used for research purposes, molecular genetic screening for 1p/19q deletions has not yet been approved for widespread use, however [4]. Future research efforts will likely investigate the applicability of genetic screening to patients with oligoastrocytomas as these tumors have also proved sensitive to PCV [5,6]. Other research efforts focus on the hypothesis that the chemosensitivity of oligo-containing tumors is not specific for PCV and ongoing clinical trials are investigating the use of temozolomide and other such agents for treatment. Suggested reading is listed below [7,8].

- References:**
- 1 - Cairncross JG, Ueki K, Zlatescu MC, et al. Specific genetic predictors of chemotherapeutic response and survival in patients with anaplastic oligodendrogliomas. *JNCI* 1998 Oct 7; Vol 90 (No. 19); 1473-9.
 - 2 - Jeuken JW, Sprenger SH, Wesseling P, et al. Identification of subgroups of high-grade oligodendroglial tumors by comparative genomic hybridization. *J Neuropathol Ex Neurol* 1999 Jun; 58 (6): 606-12.
 - 3 - Bigner SH, Matthews MR, Rasheed BK, et al. Molecular genetic aspects of oligodendrogliomas including analysis by comparative genomic hybridization. *Am J Pathol* 1999 Aug; 155(2): 375-86.
 - 4 - Smith JS, Alderete B, Minn Y, et al. Localization of common deletion regions on 1p and 19q in human gliomas and their association with histological subtype. *Oncogene* 1999 Jul 15; 18(28): 4144-52.
 - 5 - Glass J, Hochberg FH, Gurber ML, et al. The treatment of oligodendrogliomas and mixed oligodendroglioma-astrocytomas with PCV chemotherapy. *J Neurosurg* 1992;76:741-5.
 - 6 - Kim L, Hochberg FH, Thornton AF, et al. Procarbazine, lomustine, and vincristine (PCV) chemotherapy for grade III and grade IV oligoastrocytomas. *J Neurosurg* 1996; 85:602-7.
 - 7 - Cairncross JG, Macdonald DR. Successful chemotherapy for recurrent malignant oligodendroglioma. *Ann Neurol* 1988;23:360-4.
 - 8 - Kraus JA, Koopman J, Kaskel P, et al. Shared allelic losses on chromosomes 1p and 19q suggest a common origin of

oligodendroglioma nd oligoastrocytoma. J Neuropathol Exp Neurol 1995; 54:91-5.

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What's Hot in Neuro-Oncology

Volume: 1, Issue: 1

Title: Oligodendrogliomas versus Oligoastrocytomas: Recent Genetic Findings and Implications for Chemotherapy

Category: Adult Neurosurgery

Contributor(s): Tom Deisboeck, M.D., Fred H. Hochberg, M.D.

Institution: 1 Neurosurgical Service and 2 Department of Neurology, The Brain Tumor Center, Massachusetts General Hospital, Harvard Medical School Boston, MA 02114

Summary: Oligodendrogliomas and oligoastrocytomas account for about 5% of all primary brain tumors [4]. Whereas homogenous oligodendrogliomas tend to grow relatively slowly, malignant oligoastrocytomas behave much more aggressively. In fact, the prognosis worsens as the astrocytic component increases [6]. Differences between these tumor groups are also evident in the response to chemotherapy. As clinical studies have shown, malignant oligoastrocytomas respond to PCV therapy (procarbazine, lomustine (CCNU), vincristine) emphasizing the importance of the astrocytic component for treatment planning [3,4,6]. In recent years, novel genetic analyses have shed more light on the histogenetic differences - with implications for the clinical situation.

Besides the allelic loss of heterozygosity (LOH) of chromosomal arm 1p, LOH 19q is the most frequently observed genetic alteration in oligodendrogliomas and oligoastrocytomas (50 - 70%), suggesting the involvement of a putative tumor suppressor gene not only on 1p but also on 19q [1,5]. Microsatellite analyses map this gene to 19q13.3 [2,7]. Deimling v. et al. stated that LOH 19q in oligodendrogliomas and oligoastrocytomas seems to occur at an early stage of transformation and that it usually affects the entire arm of the chromosome [2]. Kraus et al. observed in their studies that all oligodendroglioma and oligoastrocytomas with LOH 1p also show LOH 19q, indicating a coincidental loss. However, LOH 19q without LOH 1p is seen in some cases as well. The authors therefore conclude that both oligodendrogliomas (WHO II) and oligoastrocytomas (WHO II) derive from a common bipotential precursor, that their tumorigenesis often involves both LOH 19q and LOH 1p, and that LOH 19q may precede LOH 1p [5]. This pathway, however, can also lead to aggressive (anaplastic) oligoastrocytomas, which harbor not only p53 mutations and LOH 17p but also losses of chromosome 9p and 10q [1,5,6].

Recently, Cairncross et al. investigated the statistical significance of such molecular events for chemosensitivity in 39 patients with anaplastic oligodendrogliomas, most of them treated according to a PCV scheme [1]. The study reveals that LOH 1p is a statistically significant predictor of chemosensitivity and that the combined LOH of both 1p and 19q is statistically significantly associated with chemosensitivity and longer recurrence-free survival after chemotherapy. In fact, 95% of these patients are alive 5 years after diagnosis. Conversely, ring-enhancement on neuroimaging and CDKN2A gene deletions (i.e. losses of chromosome 9) are associated with a significantly worse prognosis (below one year).

These results, together with the aforementioned finding of Kim et al. that anaplastic oligodendrogliomas mixed with high grade astrocytomas show similar chemosensitivity pattern [4], further support molecular analysis as a potentially very valuable tool in clinics for treatment evaluation and outcome predictions for patients with anaplastic or mixed oligodendroglial tumors.

References: 1. Cairncross J.G., Ueki K., Zlatescu M.C., Lisle D.K., Finkelstein D.M., Hammond R.R., Silver J.S., Stark P.C., Macdonald D.R., Ino Y., Ramsay D.A., Louis D.N.: Specific genetic predictors of chemotherapeutic response and survival in patients with anaplastic oligodendrogliomas. *J. Natl. Cancer Inst.* 90: 1473-1479, 1998.

2. Deimling V. A., Nagel J., Bender B., Lenartz D., Schramm J., Louis D.N., Wiestler O.D.: Deletion mapping of chromosome 19 in human gliomas. *Int. J. Cancer* 57: 676-680, 1994.

3. Glass J., Hochberg F.H., Gruber M.L., Louis D.N., Smith D., Rattner B.: The treatment of oligodendrogliomas and mixed oligodendroglioma-astrocytomas with PCV chemotherapy. *J. Neurosurg.* 76: 741-745, 1992.

4. Kim L., Hochberg F.H., Thornton A.F., Harsh G.R. IV, Patel H., Finkelstein D., Louis D.N.: Procarbazine, lomustine, and vincristine (PCV) chemotherapy for grade III and grade IV oligoastrocytomas. *J. Neurosurg.* 85: 602-607, 1996.

5. Kraus J.A., Koopmann J., Maintz D., Brandner S., Schramm J., Louis D.N., Wiestler O.D., Deimling v. A.: Shared allelic losses on chromosome 1p and 19q suggest a common origin of oligodendroglioma and oligoastrocytoma. *J. Neuropathol.*

Exp. Neurol. 54: 91-95, 1995.

6. Maintz D., Fiedler K., Koopmann J., Rollbrocker B., Nechev S., Lenartz D., Stangl A.P., Louis D.N., Schramm J., Wiestler O.D., Deimling v. A.: Molecular genetic evidence for subtypes of oligoastrocytomas. J. Neuropathol. Exp. Neurol. 56: 1098-1104, 1997.

7. Yong W.H., Chou D., Ueki K., Harsh G.R. IV, Deimling v. A., Gusella J.F., Mohrenweiser H.W., Louis D.N.: Chromosome 19q deletions in human gliomas overlap telomeric to D19S219 and may target a 425 kb region centromeric to D19S112. J. Neuropathol. Exp. Neurol. 54: 622-626, 1995.

8. Jueken, J.W.M., Sprenger, S., Wesseling, P., Macville, V.E., Deimling, A., Teepe, L.J.M., van Overbeeke, J.J., Boerman, R.H.: Identification of Subgroups of High-grade Oligodendroglial Tumors by Comparative Genomic Hybridization. J. of Neuropathol. Exp. Neurol. 58(6): 606-611, 1999.

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Featured Article

Volume: 1, Issue: 1

Title: Identification of subgroups of high-grade oligodendroglial tumors by comparative genomic hybridization

Category: Neuro-Pathology

Journal: Journal of Neuropathology and Experimental Neurology, Vol: 58, No. 6: pages 606-612, June 1999

Authors: Jeuken JWM, Sprenger SHE, Wesseling P, et al

Summary: In contrast to astrocytic tumors, approximately two-thirds of anaplastic oligodendrogliomas are reported to be chemosensitive. Relatively little is known about the genetic aberrations in oligodendroglial tumors (OTs). In order to elucidate oligodendroglial oncogenesis and to find specific genetic aberrations which may have prognostic and therapeutic implications, we performed comparative genomic hybridization (CGH) to detect chromosomal copy number changes in 17 low grade OTs (LG-OTs) and 12 high grade OTs (HG-OTs) lacking a prominent astrocytic component. In our study, loss of chromosome 1p (79%) and 19q (76%) were most frequently detected by CGH : all LG-OTs and 50% of the HG-OTs contained -1p (including 1p36-32), -19q (including 19q13.3), or both. The other 50% of HG-OTs harbored +7 and/or -10 without a loss of 1p36-32 and 19q13.3. Since losses of 1p36-32 and 19q13.3 were mutually exclusive with +7 or -10, the HG-OTs could be divided in -1p/-19q and +7/-10 tumors. While the -1p/-19q tumors can be considered as pure anaplastic oligodendrogliomas, the similarities between CGH profiles of glioblastomas (GBMs) and +7/-10 HG-OTs suggests that the latter tumors may rather be GBMs with prominent oligodendroglial differentiation. However, since patients with a +7/-10 HG-OT showed a longer survival compared to patients with a GBM, +7/-10 HG-OTs are not just simply misdiagnosed GBMs. The prognostic and possibly therapeutic relevance of this genetic subtyping of HG-OTs was indicated by survival analysis showing a shorter survival time for patients with a +7/-10 HG-OT compared to patients with a -1p/-19q HG-OT and by Cairncross et al (1998) who reported LOH 1p to be predictive for chemosensitivity. The molecular differences in the group of HG-OTs are the result of the notoriously difficult problem to clearly distinguish these tumors on the basis of histopathological examination. We conclude that CGH is a powerful tool to assist in the identification of two major subgroups of HG-OTs with prognostic and possibly therapeutic relevance.

References: Cairncross et al. Specific genetic predictors of chemotherapeutic response and survival in patients with anaplastic oligodendrogliomas. Journal of the National Cancer Institute, Vol 90, No. 19, 1998
von Deimling A, Teepen HLJM, van Overbeeke JJ, Boerman RH

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Featured Article

Volume: 1, Issue: 1

Title: Treatment of patients with primary glioblastoma multiforme with standard postoperative radiotherapy and radiosurgical boost: prognostic factors and long-term outcome.

Category: Adult Neurosurgery

Journal: J Neurosurgery, Vol: 90, No. 1: pages 72-77, Jan. 1999

Authors: Shrieve DC, Alexander E 3rd, Black PM, Wen PY, Fine HA, Kooy HM, Loeffler JS.

Summary: Aggressive local treatment, eg. surgery and radiosurgery, remains the most effective approach in combating glioblastomas and prolonging quality life in our patients. Our published series in 1999 reflected the effect of adding radiosurgical treatment to conventional surgical resections in a series of 78 patients with glioblastoma multiforme as their original diagnosis treated from 1988 through 1997. Six of the 13 patients alive at the time of that analysis in September, 1997 have died over the ensuing 25 months. Seven survive, six with no evidence of recurrence (survival 28-95 months from diagnosis, median 68 months) (ages 14-50 years at time of radiosurgery, median 37). The seventh survivor is not responding to chemotherapy, now 28 months from diagnosis.

Local therapy is not expected to cure a diffuse disease. However, by greatly enhancing the log kill of this malignant tumor, using aggressive surgical resection followed by a very effective tumoricidal therapy (radiosurgery), significant survival benefit is gained. The very invasive nature of some of these tumors renders this approach useless in some patients, but the median life expectancy and preservation of quality is enhanced in the patient population at large, providing double to triple the survival advantage conferred by the best alternate treatment. Until we have useful treatment for the invasive tumor cells, our best approach remains effective local techniques. The significant improvement in image guided surgical resection (Intraoperative MRI {MRT} [1,2], other stereotactic techniques, cortical mapping, incorporation of SPECT and MR-spectroscopy to enhance tumor definition and discrimination of radiation changes versus recurrent tumor) will probably offer significant advantage beyond the addition of radiosurgery alone in our current series of patients.

References: 1. Alexander E III, Moriarty TM, Kikinis R, Jolesz FA: Innovations in minimalism: Intraoperative MRI. *Clinical Neurosurgery* 43: 338-352, 1996.

2. Alexander E III, Moriarty TM, Kikinis R, Black P, Jolesz FM. The present and future role of intraoperative MRI in neurosurgical procedures. *Stereotact Funct Neurosurg* 68:10-17, 1997.