



# SELECT REVIEW IN NEURO-ONCOLOGY



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**Anthony L. Asher, MD**  
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**Volume 1, Issue 2**  
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Welcome to **Select Review in Neuro-Oncology**. It is our hope that this will be a valuable resource for individuals with an interest in Neuro-Oncology. Our objective is to provide a periodic summary of pertinent information in the literature related to brain tumors. A distinct and important feature of this effort is its multi-disciplinary focus. Individuals from across the country in ten different disciplines including the basic sciences have pledged their support to this effort. The **Select Review in Neuro-Oncology** is sponsored by the Joint Section on Tumors of the American Association of Neurological Surgeons and the Congress of Neurological Surgeons. Significant support for this project is provided by members of The Society for Neuro-Oncology.

Special thanks goes to the editors, staff, and advisory board members listed on this page. Their willingness to donate time and effort is essential to the success of the **Select Review in Neuro-Oncology**. Their efforts are greatly appreciated.

We will be improving and enhancing this feature over the next few issues. Your comments are appreciated. Please e-mail Tony Asher, MD at [tonyasher@cnsa.com](mailto:tonyasher@cnsa.com) with any questions or comments.

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### Adult Neurosurgery

**Title:** Stereotactic radiosurgery plus whole brain radiotherapy versus radiotherapy alone for patients with multiple brain metastases  
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# Select Review in Neuro-Oncology

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Volume: 1, Issue: 2

**Title:** Oligodendroglioma: An Appraisal of Recent Data Pertaining to Diagnosis and Treatment

**Review Type:** Article

**Category:** Adult Neurosurgery

**Journal:** Neurosurgery, Vol: 45, No. 6: pages 1279-1291, Dec 1999

**Authors:** FortinD, CairncrossGJ, Hammond RR

**Summary:** This article provides an excellent review of current data concerning the diagnosis, prognosis and treatment of oligodendrogliomas. The authors maintain that oligodendrogliomas are both underdiagnosed and chemosensitive, a supposition which suggests that a large number of glioma patients are receiving suboptimal care.

Diagnostic criteria were analyzed with the conclusion that nuclear roundness and regularity (often accompanied by an eccentric rim of cell process free eosinophilic cytoplasm) are the most reliable cytologic features of this neoplasm and thus are of more diagnostic significance than the classic criteria (fried egg and chicken wire). Other criteria are discussed. Studies using corrected criteria suggest that oligodendrogliomas might represent 25 to 33% of primary brain tumors rather than the 5% percent determined from studies utilizing classic criteria for diagnosis.

Oligodendrogliomas are chemosensitive and confer improved prognosis if present to any degree in mixed gliomas. Features of oligodendrogliomas with prognostic implication are: contrast enhancement on CT or MRI; endothelial hyperplasia; tumor morphology; mitotic activity; astrocytic component; and allelic loss in the 1p and 19q chromosome arms. Classification of oligodendrogliomas as either low or high grade is felt to be most appropriate for prognostic purposes.

The literature supports treatment of oligodendrogliomas by surgical debulking (with a goal of gross total resection where possible) followed by chemotherapy. PCV-3 (procarbazine, lomustine, vincristine) has been especially efficacious. Radiotherapy is not clearly of benefit in low grade oligodendrogliomas and should be reserved for use after surgery and chemotherapy in high grade oligodendrogliomas.

Although this article represents the opinions of the authors, the literature review is thorough and the conclusions drawn and recommendations made are persuasive.

# Select Review in Neuro-Oncology

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**Title:** Expression of Activated Epidermal Growth Factor Receptors, Ras-Guanosine Triphosphate, and Mitogen-activated Protein Kinase in Human Glioblastoma Multiforme Specimens

**Review Type:** Article

**Category:** Adult Neurosurgery

**Journal:** Neurosurgery, Vol: 45, No. 6: pages 1442-1453 , Dec. 1999

**Authors:** Feldkamp M, Lala P, et al.

**Summary:** This paper explores the significance of epidermal growth factor receptor (EGFR) amplification and mutation in GBMs. EGFRvIII, (the truncated protein resulting from a specific mutation of the EGFR gene which activates the Ras-mitogen-activated protein kinase pathway and has been shown to confer growth advantage), is expressed by as many as 62% of GBMs. The authors evaluated the expression of EGFR and EGFRvIII and EGFR activation status using immunohistochemical (IHC) analysis, Western blotting and reverse transcriptase PCR. In the small cohort of tumors examined (GBMs n=12, gliosarcomas n=2, low grade glioma n=1, non tumor control n=7) IHC results correlated fairly well with those of the other techniques and revealed EGFRvIII expression in 8 (67%) of the GBMs. EGFRvIII expression was associated with increased activation of Ras-mitogen-activated protein kinase and with decreased mean survival time.

Although the significance of the results described is limited by sample size, this article addresses an issue of increasing importance in the management of gliomas. Molecular characterization of gliomas is both feasible and germane, providing prognostic information and enabling targeted chemotherapeutic and genetic intervention.

# Select Review in Neuro-Oncology

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**Title:** Morbidity and Survival after 1,3-bis(2-chloroethyl)-1-Nitrosourea Wafer Implantation for Recurrent Glioblastoma: A Retrospective Case-matched Cohort Series

**Review Type:** Article

**Category:** Adult Neurosurgery

**Journal:** Neurosurgery, Vol: 45, No. 1: pages 17-23, July 1999

**Authors:** Subach B, Witham T, et al.

**Summary:** In an effort to determine the benefits and risks of implantation of BCNU wafers, 17 patients with recurrent GBM who underwent resection and implantation were matched retrospectively to a cohort group of 45 patients who underwent resection without implantation. Complications, especially those associated with wound healing (i.e. infection, CSF leak) were significantly higher in the implant group (13 complications in 8 patients with BCNU (n=17) vs. 8 complications in 6 patients without (n=45)). Median survival was significantly shorter in the study group (14 weeks from wafer implantation) as compared to the control cohort (54 weeks from re-operation). Outcome was worse for the study group in all respects.

Although no significant demographic or treatment differences were identified between the study group and the cohort, the authors acknowledge that treatment bias cannot be excluded as a variable in a non-randomized study. It is also interesting to note (as pointed out by one of the reviewers) that the median survival of the cohort group is not only longer than that of the study group but also far exceeds the survival reported in most GBM outcome studies (median survival 14-36 weeks) as well. This increased length of survival in the cohort eliminates (statistically) any survival benefit gained by treatment.

The results obtained conflict with those produced by the Gliadel Phase III study and the authors conclude that additional study of this treatment is warranted.

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**Review Type:** Article

**Category:** Adult Neurosurgery

**Journal:** Journal of Neurosurgery, Vol: 91, No. 5: pages 822-830, Nov 1999

**Authors:** Adachi J-I, Ohbayashi K, Suzuki T, Sasaki T

**Summary:** This article reinforces known information about the tumor-suppressor gene PTEN and its actions in glioma cells. PTEN is a well-characterized tumor suppressor gene (TSG) on chromosome 10. Because of the frequency of chromosome 10 loss of heterozygosity (LOH) in gliomas, PTEN has drawn attention for a possible role in glioma formation. Germ line mutations of PTEN lead to inherited cancer syndromes Cowden's syndrome and Bannayan-Zonana syndrome. These syndromes feature breast, thyroid and other carcinomas. PTEN is known to code for a protein and lipid phosphatase that inhibits the PI3K/Akt signalling pathway. This leads to G1 cell cycle arrest followed by apoptosis in a breast cancer cell line (Weng et al, 1999)

The current paper reports inducing exogenous PTEN expression in glioma cell lines known to have PTEN mutations. As reported in breast cancer cell lines, expression of exogenous PTEN led to cell cycle arrest at G1. Moreover, when PTEN expressing cells were cultured in the presence of extracellular matrix (ECM), there was evidence of astrocytic differentiation of the cells with formation of astrocytic cell processes. This confirms recent findings by Tamura et al. that PTEN inhibits cell migration and invasion by down-regulating integrins.

The utility of inducing PTEN expression in gliomas in vivo obviously is the million-dollar question. David James et al. looked at 135 gliomas and checked for p53, p16, and PTEN mutations. PTEN mutation was only found in 30.3% of WHO grade 4 astros and only 4.8% of WHO Grade III astros. Zhou et al. looked for PTEN mutations in 44 patients with suspected familial glioma syndromes and found none. Many did have p53 mutations.

Studies like this contribute obviously to the genetic dissection of gliomas. The more tumor suppressor genes are identified, the more opportunities there will be to restore lost functions and hopefully induce gliomas to undergo apoptosis or differentiate to more benign tissue.

**References:** Weng LP et al., Cancer Research 59: 5808-5814, 1999

Zhou XP et al., Annals of Neurology 46:913-916, 1999

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**Title:** Inhibition of NF2-negative and NF2-positive primary human meningioma cell proliferation by overexpression of merlin due to vector-mediated gene transfer

**Review Type:** Article

**Category:** Adult Neurosurgery

**Journal:** Journal of Neurosurgery, Vol: 91, No. 1: pages 85-92, July 1999

**Authors:** Ikeda K, Saeki Y, et al.

**Summary:** The protein merlin, or schwannomin, is the target of inactivating mutations of the NF2 gene. Mutations of NF2 have also been identified in meningiomas, schwannomas and mesotheliomas of patients without NF2. Merlin is thought to be an important mediator of proliferation of schwann and meningeal cells, an action that may be related to alterations in actin filament assembly. Viral transfection of the NF2 gene into meningioma cells was assessed in this paper for its effect on the proliferation of 2 NF2-negative (SB, SJ) and one NF2-positive (MN 13) cell line.

Three viral vectors were studied: HSV amplicon vector; adenoviral vector (ADV) and; a retroviral vector (RV) derived from the MFG backbone. Each cell line was infected with each vector using a multiplicity of infection of 1 for the RV and HSV and 100 for ADV. Proliferation assays showed a decrease in cell numbers at 4 - 8 days and Lac-Z reporter gene expression was highest with HSV amplicon infected cell than with the other two vectors. Subsequent NF2 transfection experiments were carried out using HSV amplicon on cell lines SB and MN13. Western blots showed increased merlin production by transfected cell lines. IN the NF2 negative cell line SB cell proliferation was decreased 30-50% six days after transfection and 15-30% in the NF2 positive cell line MN13. FACS analysis suggested a higher percentage of transfected cells in G1 and the percentage of apoptotic cells was not increased.

These results suggest that NF2 overexpression is associated with G1 arrest as a mechanism for reduced cell proliferation in transfected meningioma cells. Gene transfer technologies may be well suited to the treatment of meningiomas, whose blood supply comes mainly from the external carotid, whose endothelial cells do not contain tight junctions and whose intercellular connections are abundant.

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**Title:** Accelerated fractionated proton/photon irradiation to 90 cobalt gray equivalent for glioblastoma multiforme: results of a phase II prospective trial

**Review Type:** Article

**Category:** Adult Neurosurgery

**Journal:** Journal of Neurosurgery, Vol: 91, No. 2: pages 251-260, Aug. 1999

**Authors:** Fitzek MM, Thornton AF, et al.

**Summary:** This single institution study was designed to answer the question of whether dose escalation to 90 cobalt gray equivalent (CGE) with conformal protons and photons in accelerated fractionation would improve local control. Twenty-three patients were enrolled in the study. The patients were to receive 1.8 CGE twice a day. The median proton dose was 57.6 CGE. The median age was 51 years and median KPS 90. Surgical resection was gross total in 10 patients by imaging. Treatment was generally well tolerated. All but one patient required steroids for clinical deterioration.

Median survival for the entire group was 20 mo. after first surgery and 18.6 mo. after radiation. The survival rates at 1, 2, and 3 years were 78%, 34% and 18%. The median patient survival time while maintaining a KPS score of 70 or higher was 12 mo. The actuarial rates for this quality survival at 1 and 2 years were 50% and 8%. New enhancement developed in all patients in imaging follow-up with a median time to imaging change of 8 mo. Fifty-seven percent of patients underwent at least one reoperation and the majority of specimens showed necrosis only.

The discussion of results in this paper is fair and frank. The authors compare their results to other forms of focal therapy, namely brachytherapy and radiosurgery. They comment that "the overall results are rather disappointing. The survival times curve has shifted to the right without an indication of a substantially higher plateau. This indicates delay of death rather than a higher rate of cure and this is achieved only with additional surgery in some cases and progressive disability...". The Boston and Loma Linda sites are the only 2 operational proton beam facilities currently available for patients making recruitment of these studies difficult. Future efforts to improve results might be directed at ways to reduce radiation toxicity.

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**Review Type:** Article

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**Journal:** Journal of Neurosurgery, Vol: 91, No. 4: pages 563-568, Oct. 1999

**Authors:** Huang CF, Kondziolka D, et al.

**Summary:** Brainstem metastases are difficult to treat and surgical removal is most often not an option. Focused radiosurgical treatment is an option but clinicians may be reluctant to treat metastases in this location because of fear of complications. The Pittsburg group identified 26 patients from a group of 421 in their database who were treated for 27 brainstem metastases. Twenty-one tumors were in the pons and 6 in the midbrain. Fourteen patients had other brain metastases. Twenty patients presented with brainstem signs. Twenty-four patients received whole brain irradiation and 12 underwent additional chemotherapy or immunotherapy. The median treatment volume was 1.1 ml and median marginal dose 16 Gy (range 12-20 Gy). An average of 2.5 isocenters (range 1-7) was required for coverage. Median follow-up was 9.5 mo. (range 1-43 mo.). Local control was achieved in 95% of treated lesions in 21 patients who had imaging follow-up. Complete response in 23.8%, partial in 61.9% and stabilization in 14.3%. No patient developed a new neurologic deficit from tumor growth after radiosurgery. Four patients had acute toxicity symptoms (nausea, vomiting, dizziness) hours after treatment that resolved. Neuroimaging revealed no evidence of delayed radiation toxicity in any patient. Fifty percent of those who presented with brainstem signs had marked improvement, and in 8 of these 10 the improvement was maintained. Median survival time was 11 mo. after diagnosis and 9 mo. after radiosurgery. The only factor on multivariate analysis predictive of a poorer outcome was active systemic disease.

Patients with brainstem as the only site for metastasis had a median survival of 7.3 mo. compared to 10 mo. for those with multiple metastases. The authors have demonstrated that radiosurgery is well tolerated for tumors in the brainstem and provides neuroimaging tumor control equivalent to supratentorial locations. In selected patients they recommend WBRT and radiosurgery for patients with brainstem metastases for providing prolonged tumor control and extending survival.

# Select Review in Neuro-Oncology

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

Volume: 1, Issue: 2

**Title:** Cell Cycle arrest and astrocytic differentiation resulting from PTEN expression in glioma cells

**Review Type:** Article

**Category:** Adult Neurosurgery

**Journal:** Journal of Neurosurgery, Vol: 91, No. 5: pages 822-830, Nov. 1999

**Authors:** Adachi J, Ohbayashi K, et al.

**Summary:** The PTEN gene shares homology with tensin, a cytoskeletal protein that interacts with actin filaments at focal adhesions and the gene that encodes this protein possesses intrinsic protein tyrosine phosphatase activity. PTEN behaves as a tumor suppressor gene and it has been suggested that PTEN can negatively regulate cell proliferation by antagonizing protein kinase-mediated signaling. The gene has been isolated to the 10q23.3 region of chromosome 10. While PTEN deletions have been shown in malignant glioma cell lines and tumors, inactivation is infrequent in low grade gliomas, suggesting that PTEN mutations are critical to the process of glioma progression. In this study the authors transfected 4 malignant glioma cell lines with a tetracyclin controlled inducible PTEN gene expression system. Colony forming efficiency was reduced in transfected lines to 15-33% of control values. Western blot analysis confirmed inducibility of the gene product by tetracyclin. Growth curve analysis revealed suppression of growth with activation of the PTEN gene. Morphologic features of differentiation to a more normal phenotype were also seen in transfected cells. FACS analysis revealed G1 arrest in transfected cell lines. Distinct changes of Rb phosphorylation were not seen on Western blot analysis. GFAP expression was increased in transfected cell lines grown on Matrigel. These findings indicate that exogenous PTEN expression inhibits the proliferation of glioma cells by inducing G1 arrest and elicits astrocytic differentiation in the presence of ECM. They also suggest that the G1 arrest produced by PTEN may occur independently of the Rb signal transduction pathway.

# Select Review in Neuro-Oncology

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

Volume: 1, Issue: 2

**Title:** Noninvasive evaluation of the malignant potential of intracranial meningiomas performed using proton magnetic resonance spectroscopy.

**Review Type:** Article

**Category:** Adult Neurosurgery

**Journal:** Journal of Neurosurgery, Vol: 91, No. 6: pages 928-934, Dec. 1999

**Authors:** Shino A, Nakasu S, et al.

**Summary:** Magnetic resonance spectroscopy (MRS) has shown promise with its ability to predict the grade or clinical behavior of intra-axial glial neoplasms based on choline, creatine, glutamate, lactate and lipid spectral peaks and ratios. Ten to 15% of meningiomas are malignant and a variety of radiographic features have been correlated with histology. The authors studied the MIB-1 labeling index and MRS patterns in 29 meningioma patients. Twenty-four were benign, 4 atypical and 1 malignant. The mean MIB-1 labeling index was significantly higher in the non-benign meningioma group. There was a strong relationship between the MIB-1 index and the Cho/Cr ratio ( $P < 0.001$ ). The Cho/Cr ratios were significantly higher in the non-benign versus benign group ( $P = 0.0002$ ). A methylene signal was seen in 4 of 5 meningiomas from the non-benign group. When lactate signal was seen it occurred in 3 atypical and 2 benign meningiomas, the latter with MIB-1 indices higher than for the benign group mean. These results suggest a role for the evaluation of meningiomas using MRS and that the Cho/Cr ratio may predict histology. In addition a methylene and/or lactate peak suggests a high grade tumor.

# Select Review in Neuro-Oncology

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

Volume: 1, Issue: 2

**Title:** Predicting the probability of meningioma recurrence based on the quantity of peritumoral brain edema on computerized tomography scanning

**Review Type:** Article

**Category:** Adult Neurosurgery

**Journal:** Journal of Neurosurgery, Vol: 91, No. 3: pages 375-383, Sept. 1999

**Authors:** Mantle RE, Lach B, et al.

**Summary:** Radiographic features of meningiomas on CT or MR imaging studies have been correlated with pathologic type, grade, the likelihood of recurrence, the degree of pial blood supply and levels of various cytokines in tumor tissue. In this study the authors sought to determine whether the quantity of peritumoral edema could be correlated with both brain invasion by tumor and subsequent tumor recurrence. CT scans on 124 cases were available for review from a tumor population of 135 patients treated over 19 years at the Ottawa Civic Hospital. Resections were classified as complete or incomplete. Follow-up beyond 4 years after surgery was conducted mainly by telephone interview. Edema "grade" was the measurement in cm. of the greatest extent of edema beyond the tumor margin on the axial slice showing the most tumor. Validation of "edema grade" was performed in 27 cases by digitizing images and measuring volumes of edema. Tumors were classified by the W.H.O. criteria. The overall recurrence rate was 32%, 14% after complete resection and 76% after incomplete resection. The mean follow-up was 9 +/- 4 yrs. Malignant tumors comprised 8% of cases. Peritumoral edema grade correlated linearly with the chance of brain invasion, which increased 20% for each centimeter of edema ( $P < 0.0001$ ). Edema grade correlated with recurrence after complete resection using the equation (edema grade)<sup>3</sup> X 0.7 ( $r=1$ ,  $p<0.0001$ ). Multivariate analysis revealed the completeness of tumor resection, edema grade and brain invasion to be significant predictors of tumor recurrence. The presence of brain invasion on histology was predictive of recurrence after complete resection with an accuracy of 83%, a sensitivity of 89% and a specificity of 82%. Based on this data the authors recommended that neuroradiologists report an edema grade and that in those tumors with edema measuring more than 1 cm. surgeons might consider providing a "resection margin" to lessen the chance of recurrence. Follow-up times of 20 yrs. maximum and 10 yrs. minimum were recommended.

# Select Review in Neuro-Oncology

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

Volume: 1, Issue: 2

**Title:** Dominant-negative mutations of the tumor suppressor p53 relating to early onset of glioblastoma multiforme

**Review Type:** Article

**Category:** Basic Science

**Journal:** Cancer Research, Vol: 59, No. : pages 4765-4769, Oct.1999

**Authors:** Marutani M, Tonoki H, Tada M, Takahashi M, Kashiwazaki H, Hida Y, Hamada J, Asaka M, Moriuchi T.

**Summary:** Previous research suggests that some mutant forms of p53 are able to inactivate the endogenous wild-type p53 protein in a dominant-negative fashion by forming a heterotetramer complex. In contrast to tumors harboring other recessive p53 mutations, those tumors bearing dominant-negative mutations should be able to inactivate the normal p53 protein. Thus, the consequent inhibition of normal p53 function should promote tumor development in a shorter period of time. To test this hypothesis, the authors developed a yeast-based assay for the assessment of dominant-negative potential of p53 mutants. The transdominance assay consists of a yeast strain containing an integrated reporter ADE2 gene under the control of a p53-responsive promoter. The yeast were transformed with two plasmids, one a wildtype p53 and the second a mutant p53, both driven by an ADH1 promoter. The yeast were grown on medium lacking leucine and tryptophan. In the presence of a dominant-negative mutant p53 protein, the wild-type p53 protein was prevented from binding to the p53-responsive element in the ADE2 promoter and the yeast colony was red due to the accumulation of an intermediate of adenine synthesis. In this report, the authors tested a total of 106 p53 mutants that were identified in brain tumors, breast cancers, premalignant lesions and squamous cell carcinomas of the oral epithelium, or otherwise created by mutagenesis. The authors then measured the differences in the age of onset according to the transdominance potential of the p53 mutations in the tumor patients. For 40 patients with sporadic glioblastoma, the average age at onset was  $30.4 \pm 14.7$  years in patients with dominant-negative mutations, which was significantly younger than that of patients with recessive mutations ( $55.2 \pm 18.6$  years) or no mutations ( $54.7 \pm 17.1$  years). Significant differences were not observed between patients with anaplastic astrocytomas or tumors of other cancer types. The authors conclude that the dominant-negative p53 mutants accelerate development and/or growth of glioblastoma multiforme and are related to the earlier onset of brain tumors.

# Select Review in Neuro-Oncology

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

Volume: 1, Issue: 2

**Title:** Development of a flexible and specific gene delivery system for production of murine tumor models

**Review Type:** Article

**Category:** Basic Science

**Journal:** Oncogene, Vol: 18, No. : pages 5253-5260, 1999

**Authors:** Fisher GH, Orsulic S, Holland E, Hivley, WP, Li Y, Lewis BC, Williams BO and Varmus HE

**Summary:** In this review the authors summarize their development of new mouse models of human tumors, with the first to be developed being a glioma model. These models are based on selectively introducing oncogenes into glial cells in the adult mouse brain using replication incompetent avian retroviruses, which normally do not infect rodent cells. The key is that the investigator determines which cells in the animal are susceptible to infection, by expressing the receptor for avian retrovirus from a cell-type specific promoter. In the case of glial cells, GFAP and nestin have been used, allowing infection of more differentiated astrocytic glia and more immature precursor cells, respectively. The power of the system comes from three characteristics: first, combinations of genes can be introduced easily simply by mixing several viruses together prior to injection; second, the target cells are adult glia, as is presumed to be the case in human tumors, rather than developing cells, as would be the case in a standard transgenic animal; thirdly, this system is easily combined with tumor suppressor gene knockout animals by interbreeding, allowing one to assemble a considerable part of the molecular spectrum of a tumor in a single animal. This model therefore holds the potential of dissecting molecular pathways in vivo - one step closer to the human disease, and yet controllable in an elegant way.

# Select Review in Neuro-Oncology

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

Volume: 1, Issue: 2

**Title:** FasL (CD95, Apo1L) is expressed in the normal rat and human brain: Evidence for the existence of an immunological brain barrier.

**Review Type:** Article

**Category:** Basic Science

**Journal:** Glia, Vol: 27, No. 1: pages 62-74, July 1999

**Authors:** Bechmann I, Mor G, Nilsen J, Eliza M, Nitsch R, and Naftolin F.

**Summary:** Preemptive elimination of auto-reactive T-lymphocytes, which percolate into the brain, would help account for the immune privileged status this organ demonstrates. Using RT-PCR, Bechmann demonstrates that normal, healthy rat and human brain tissues express the Fas-L gene, which is a potent activator of apoptosis in cells expressing its receptor, Fas. T-lymphocytes, which extravasate from blood vessels, express Fas and undergo apoptosis when encountering FasL. (The notable exception being T-lymphocytes reactive against myelin basic protein, which are resistant to apoptosis-induction by FasL). Use of admittedly controversial polyclonal antibodies against FasL (N20 and Q20), (and copious control experiments) positioned the investigators to demonstrate by immunohistochemistry that both neurons and astrocytes express this death-activator. A predilection toward perivascular localization of the FasL-expressing cellular processes was also noted. Functional studies in situ using a needle-wound experiment, and in vitro using primary or secondary cultures of brain cells, demonstrated induced apoptosis of FasL-responsive lymphocytes. Subversion of an immune response by the specific apoptosis-inducing ligand, FasL, argues for an Immunological Brain Barrier in addition to the anatomical Blood Brain Barrier. Whether this contributes to the mechanism by which primary brain neoplasms escape immune detection remains to be demonstrated, but raises an interesting challenge to treatment strategies based on immune cell activation and recognition of tumor antigens.

# Select Review in Neuro-Oncology

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

Volume: 1, Issue: 2

**Title:** Creation of human tumour cells with defined genetic elements

**Review Type:** Article

**Category:** Basic Science

**Journal:** Nature, Vol: 400, No. 6743: pages 464-468, July 29, 1999

**Authors:** Hahn WC, Counter CM, Lundberg AS, Beijersbergen RL, Brooks MW, Weinberg RA

**Summary:** ABSTRACT: During malignant transformation, cancer cells acquire genetic mutations that override the normal mechanisms controlling cellular proliferation. Primary rodent cells are efficiently converted into tumorigenic cells by the coexpression of cooperating oncogenes. However, similar experiments with human cells have consistently failed to yield tumorigenic transformants, indicating a fundamental difference in the biology of human and rodent cells. The few reported successes in the creation of human tumour cells have depended on the use of chemical or physical agents to achieve immortalization, the selection of rare, spontaneously arising immortalized cells, or the use of an entire viral genome. We show here that the ectopic expression of the telomerase catalytic subunit (hTERT) in combination with two oncogenes (the SV40 large T oncoprotein and an oncogenic allele of H-ras) results in direct tumorigenic conversion of normal human epithelial and fibroblast cells. These results demonstrate that disruption of the intracellular pathways regulated by large T, oncogenic ras and telomerase suffices to create a human tumor cell.

**REVIEW:** It took over a decade to accomplish the feat described in this seminal report in cancer biology. The addition of telomerase to T-antigen and ras expression was needed to convert a normal human epithelial or fibroblast cell into a "full-blown" tumor cell line. T-antigen has been shown to inactivate both the retinoblastoma (pRB) and p53 tumor suppressor proteins and one might thus argue that malfunctions in any protein/gene involved in the normal homeostatic mechanisms of these four biochemical pathways (ras, p53, p16/pRB, and telomerase) would lead to human cellular tumorigenesis. However, it is yet unclear if T antigen also disrupts additional cellular functions and the possibility thus exists that additional human oncogenic pathways may be required for transformation. Now that the key component pathways in tumorigenesis have been identified in vitro, it will be interesting to determine if components of other pathways lead to a similar effect and if similar findings can be replicated in vivo.

# Select Review in Neuro-Oncology

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

Volume: 1, Issue: 2

**Title:** Regional treatment of epidermal growth factor receptor VIII-expressing neoplastic meningitis with a single-chain immunotoxin, MR-1.

**Review Type:** Article

**Category:** Basic Science

**Journal:** Clinical Cancer Research, Vol: 5, No. 9: pages 2646-52, Sept. 1999

**Authors:** Archer GE. Sampson JH. Lorimer IA. McLendon RE. Kuan CT. Friedman AH. Friedman HS. Pastan IH. Bigner DD.

**Summary:** The incidence of neoplastic meningitis is on the rise. Neoplastic meningitis can result from a direct seeding of the neuraxis by primary brain tumors or by hematogenous spread of systemic solid tumors. A frequent genetic alteration in primary brain tumors such as gliomas is an in frame deletion in the epidermal growth factor receptor gene (EGFRvIII), which brings together what were normally distant polypeptide sequences in the intact receptor. A novel glycine is formed at the fusion junction resulting in a unique and tumor-specific target. Using phage display we have isolated a single chain antibody specific for the EGFRvIII mutation, MR-1. As the toxic element of the MR-1 immunotoxin we have chosen a genetically modified Pseudomonas exotoxin. The bacterial Pseudomonas exotoxin is highly toxic to mammalian cells. It is estimated that a single molecule is all that is required to cause cell death. The Pseudomonas exotoxin normally contains 3 protein domains, domain 1 is responsible for cell binding. For the production of the MR-1 immunotoxin we have eliminated domain 1 and replaced it with the sequence coding for the single chain antibody MR-1 forming the immunotoxin MR1scFvPE38KDEL (MR-1 immunotoxin). We studied the therapeutic efficacy of MR-1 immunotoxin in an athymic rat model of neoplastic meningitis. In this model tumors are initiated and therapy is given through an indwelling subarachnoid catheter. In all experiments MR-1 immunotoxin was given every other day for a total of three doses. The maximally tolerated dose in non-tumor bearing rats was three doses of 3 &#61549;g. For therapeutic studies the target was neoplastic meningitis induced by intrathecal inoculation of the EGFRvIII expressing human glioma U87MG.&#61508;EGFR. A dose escalation study compared the survival of three equal doses of 1, 2, and 3 &#61549;g of MR-1 immunotoxin with saline or 3 &#61549;g of the control immunotoxin specific for the IL-2 receptor, anti-Tac. All animals treated with three doses of saline or 3 &#61549;g of anti-Tac died with median survival of 7 and 10 days, respectively. There were 75% (6/8) long term survivors (LTS) in the group treated with three doses of 1 &#61549;g, and 57% (4/7) LTS in the groups treated with three doses of either 2 or 3 &#61549;g of MR-1 immunotoxin. None of the MR-1 immunotoxin treated groups reached median survival by the termination of the study at 53 days. Therefore, median survival was estimated to be greater than 53 days resulting in an estimated increase in median survival of >657% compared with saline and 430% versus anti-Tac. Compartmental therapy with 3 doses of 2 &#61549;g of MR-1 immunotoxin is effective in the treatment of EGFRvIII expressing neoplastic meningitis. This dose was found to have no clinical or histopathological effects on non-tumor bearing animals. MR-1 immunotoxin is therefore considered specific and safe within its therapeutic window. Phase I clinical trials for tumors invading the intrathecal space which express the EGFRvIII target should be initiated.

# Select Review in Neuro-Oncology

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

Volume: 1, Issue: 2

**Title:** Local and Sustained Delivery of 5-Fluorouracil from Biodegradable Microspheres for the Radiosensitization of Glioblastoma. A Pilot Study.

**Review Type:** Article

**Category:** Medical Oncology

**Journal:** Cancer, Vol: 86, No. 2: pages 325-30, July 15, 1999

**Authors:** Menei P, Venier M-C, Gamelin E, et al

**Summary:** Implantable biodegradable poly(D,L lactide-co-glycolide) (PLAGA) microspheres were used as a vehicle to provide 5-fluorouracil (5-FU) brachytherapy at the time of initial surgical resection in eight patients with glioblastoma. These microspheres were uniformly implanted along the walls of the surgical resection cavity at a depth of 2 cm. To potentially take advantage of 5-FU's capacity as a radiosensitizing agent, each subject was initiated on a standardized treatment regimen of involved field radiation within 7 days of surgery (total dose of 59.4 Gy in 33 1.8 Gy fractions). 5-FU dose escalation beyond 132 mg was not attempted as one patient in this dosage group experienced brain edema resulting in a 15 day radiation treatment delay. No other neurologic complications were reported, however. Median survival was 98 weeks from the time of implantation. Specifically, three patients given a 32 mg dosage died at 61, 114, and 125 weeks while three patients given the 132 mg dosage died at 31, 59, and 82 weeks, respectively. Notably, two patients from the 132 mg group did exhibit continued radiographic remission at 139 and 153 weeks, respectively. Correlative 5-FU assays confirmed sustained concentrations in the CSF for at least 1 month and blood levels that were low and transiently detectable.

# Select Review in Neuro-Oncology

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

Volume: 1, Issue: 2

**Title:** Multicenter Phase II Trial of Temozolomide in Patients with Anaplastic Astrocytoma or Anaplastic Oligoastrocytoma at First Relapse

**Review Type:** Article

**Category:** Medical Oncology

**Journal:** Journal of Clinical Oncology, Vol: 17, No. : pages 2762-71, 1999

**Authors:** Yung WKA, Prados MD, Yaya-Tur R, et al

**Summary:** A multicenter phase II trial was conducted to investigate the efficacy of temozolomide for treatment of patients with either their first recurrence of anaplastic astrocytoma (AA) (n=97) or anaplastic mixed oligoastrocytoma (AOA) (n=14). A total of 162 patients were enrolled with intent to treat (ITT). Progression-free survival (PFS) at 6 months was the primary endpoint of the study with secondary endpoints including PFS at 12 months, overall survival, and quality of life (QOL). At enrollment, median age was 42 years and 67% had a KPS of > or = 80. Notably, 60% of patients had received prior treatment with a nitrosourea compound.

A standard temozolomide dosage scheme of 200 mg/m<sup>2</sup> daily (days 1-5 inclusive) / 28 day cycle in chemotherapy naive patients and 150 mg/m<sup>2</sup> for cycle 1 escalating to 200 mg/m<sup>2</sup> for subsequent cycles thereafter (if no major adverse events). The PFS at 6 months was 46% and 24% at 12 months. Overall survival at 6 months was 75% and 56% at 12 months. A median overall PFS was reported to at 5.4 months. Objective radiographic response rates of the ITT population were complete response (CR) 8%; partial response (PR) 27%; stable disease (SD) 26%. Health-related QOL benefits using were demonstrated using two instruments (QLQ-C30 and BCM-20). Only baseline KPS was shown to be a significant prognostic factor for PFS and overall survival. For the 13 CR patients (8%), PFS was 11 to >24 months. Treatment related adverse events were easily manageable, by and large.

It is astonishing to note that 51 of 162 patients were excluded from this trial based on variation of histology interpretation. This prompts one to reconsider the validity of prior Neuro-Oncology trials with no central pathology review. Interestingly, there was no difference in efficacy when comparing patients with AA or AOA, which suggests that temozolomide has some efficacy in the more difficult to treat and traditionally less chemosensitive AA patient population. It is probably safe and reasonable to treat anaplastic glioma patients with temozolomide prior to administration of radiation (neoadjuvant treatment), although this issue has not yet been formally elucidated. Pros to neoadjuvant therapy may include more favorable vascular access to tumor and lack of radiation treatment bias obfuscating assessment of drug efficacy. Low risk of irreversible myelotoxicity also speaks to using this agent up front / first choice. Cons include prolongation to time of receiving radiation, a treatment which is clearly effective. Finally, the rationale of the 5 day on / 23 day off temozolomide regimen, pharmacokinetically speaking, is somewhat unclear. This drug needs to be investigated at higher doses and using more aggressive dosing schemes.

# Select Review in Neuro-Oncology

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

Volume: 1, Issue: 2

**Title:** Antiapoptotic Bcl-2 Family Protein Expression Increases with Progression of Oligodendroglioma

**Review Type:** Article

**Category:** Medical Oncology

**Journal:** Cancer, Vol: 86, No. 9: pages 1832-9, Nov 1, 1999

**Authors:** Deiningner MH, Weller M, Streffer J, Meyermann R

**Summary:** Bcl-2 family protein expression was examined in oligodendroglioma (Oligo) and anaplastic oligodendroglioma (AO) specimens to delineate protein accumulation during disease progression and to search for protein expression patterns predictive of time to progression and overall survival. Bcl-2 family proteins are protooncogenes that determine apoptotic cell death and proliferation in a wide range of human neoplasms. The three main Bcl-2 subfamilies include Bcl-2 (promote cell survival), BAX and BH3 (induce apoptosis).

Twenty-six de novo Oligo specimens (WHO grade 2) and 16 de novo AO specimens (WHO grade 3) were reviewed. Post-operatively (post-op), seven patients (pts) with Oligo received radiotherapy (RT) and 19 pts received no further treatment. In the AO group, 13 pts received post-op RT, 3 received post-op RT + nitrosourea based chemotherapy, and 3 received no further treatment. Nineteen pts with Oligos demonstrated 'clinical' or 'radiographic' recurrence (10 as Oligos and 9 as higher grade lesions) as did 8 pts with AO (5 as AO and 3 as GBM). In pts with Oligo, mean time to progression (MTP) was 53.4 months and mean survival (Surv) was 86.6 months while in pts with AO, MTP was 23.9 months and Surv was 24.1 months. Patient age, extent of resection, nor tumor localization had a significant impact on disease progression or overall survival in this study.

Higher Bcl-2, lower MIB-1, and lower in-situ nick translation scores were noted in Oligo pts when compared with AO pts. In Oligos, low numbers of Bax positive cells correlated with short time to disease progression. In AOs, low numbers of Bcl-2 positive cells correlated with short patient survival. In tumors that had progressed from AO, significantly more Bcl-X (Bcl subfamily), Mcl-1 (Bcl subfamily), and Bax positive cells were discovered. The authors concluded that from these data that progression of oligodendroglioma is associated with enhanced expression of Bcl-2 family proteins.

The Bcl-2 family proteins join other genetic / molecular markers reported to have clinical significance in patients with oligodendroglioma such as 1p19q deletion, EGFR overexpression, p53 accumulation, and CDK4 amplification. While provocative, the clinical data in this article require further analysis and confirmation. Specifically, no definitions for clinical or radiographic progression were provided and different treatments used at different dosages in different subsets of patients make it difficult to fully buy into the clinical applicability of Bcl-2 family proteins as of yet. It will be interesting to see the Bcl-2 markers tested in a larger and clinically homogeneous database and perhaps correlated with 1p19q deletion in Oligos and OA.

# Select Review in Neuro-Oncology

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

Volume: 1, Issue: 2

**Title:** Intracranial Fatigable Ptosis

**Review Type:** Article

**Category:** Neuro-Ophthalmology

**Journal:** Journal of Neuro-Ophthalmology, Vol: 19, No. 4: pages 257-259, Dec. 1999

**Authors:** Kao Y, Lan M, Chou M, et al

**Summary:** Two patients sought treatment for bilateral fatigable ptosis; one patient had a hematoma, and the other patient had an intracranial metastasis (gastric adenocarcinoma). Compression of the central caudal nucleus in the dorsal midbrain is proposed as the cause of this ptosis, and an alteration of central acetylcholine neurotransmission may contribute to ocular fatigability. In each case, a neostigmine test produced transient resolution of the ptosis, but results of acetylcholine receptor antibody and chest CT were negative. Because symptoms that suggest fatigable ptosis can be similar to those that suggest ocular myasthenia gravis, a careful evaluation is necessary to avoid misinterpretation.

# Select Review in Neuro-Oncology

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

Volume: 1, Issue: 2

**Title:** Postpartum Cerebellar Herniation in von Hippel-Lindau Syndrome

**Review Type:** Article

**Category:** Neuro-Ophthalmology

**Journal:** American Journal of Ophthalmology, Vol: 128, No. 3: pages 387-389, Sep. 1999

**Authors:** Othmane IS, Shields C, Singh A, et al

**Summary:** A 21 year-old female with von Hippel-Lindau syndrome was found on routine ocular examination to have severe papilledema 1 week after giving birth. MRI of the brain showed hydrocephalus from a large cerebellar cyst compressing the fourth ventricle and cerebral aqueduct. A small hemangioblastoma along the outer aspect of the cyst was noted. Herniation of the cerebellar tonsils was noted. The patient underwent urgent neurosurgical decompression with excision of the tumor and cystic mass. She recovered and did well. This case report concludes that worsening of intracranial hemangioblastoma during pregnancy in cases of von Hippel-Lindau syndrome should be realized and periodic neurologic and ophthalmologic observation is warranted.

# Select Review in Neuro-Oncology

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

Volume: 1, Issue: 2

**Title:** Genetic Alterations in Pediatric High-Grade Astrocytomas

**Review Type:** Article

**Category:** Neuro-Pathology

**Journal:** Human Pathology, Vol: 30, No. 11: pages 1284-1290, Nov. 1999

**Authors:** Yue Cheng,MB;Ho-Keung NG;Shang-Fu,Z, et.al.

**Summary:** Twenty-four pediatric high grade astrocytomas (11 AA, 13 GBM) were investigated for molecular genetic abnormalities. In contrast with adult high grade astrocytomas, no epidermal growth factor receptor amplifications and a very low percentage of PTEN mutations (2/24) were identified. As has been previously reported, P53 mutations were found in a very high percentage of brain stem astrocytomas (5/7). P53 mutations were also present in 4 out of 17 non-brain stem astrocytomas. In spite of this relatively high incidence of P53 mutations, none of these tumors were considered to be secondary, i.e., showed clinical or pathologic evidence of progression from low to high grade. Microsatellite instability was detected in 4 out of the 9 cases studied. These results indicate a somewhat different spectrum of molecular genetic abnormalities in pediatric astrocytomas compared with their adult counterparts.

# Select Review in Neuro-Oncology

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

Volume: 1, Issue: 2

**Title:** Chondrosarcoma of the Base of the Skull

**Review Type:** Article

**Category:** Neuro-Pathology

**Journal:** Am J Surg Pathol, Vol: 23, No. 11: pages 1370-1378, Nov, 1999

**Authors:** Rosenberg AE, Nielsen GP, Keel SB, Renard LG, Fitzek MM, et al

**Summary:** The authors report their experience with surgery and proton beam irradiation of 200 patients with chondrosarcoma (CSA) of the skull base. Most were located near the temporo-occipital junction (66%). Most were histologically mixed hyaline and myxoid (63%), about 30% were hyaline, the remainder pure myxoid. Significantly, the diagnosis was changed from the interpretation of chordoma by a referring institution in 74 of the patients. Immunohistochemistry revealed none diagnosed as CSA were positive for cytokeratin (AE1/3, Cam 5.2), 99% were positive for S100, and about 8% showed faint EMA positivity. Surgery was biopsy or partial resection (21%), subtotal (74%), and gross total (5%). All received post surgical fractionated precision conformal RT from 64.2-79.6 CGE, in 38 fractions. With a mean follow-up of 65 months, there were three local recurrences, no metastases, and two deaths from tumor local recurrence. Both 5 and 10 yr survivals were 99%. This was compared to progression-free survivals of "similarly aggressively treated" pts with chordoma at their institution of 70% and 45%. Points raised were the apparent difference in survival of CSA vs chordoma and relatively high rate of discordance in pathologic diagnosis. No case controlled therapy group is paired with the patients, and the study does not address morbidity associated with the therapy or neurologic status/quality of life measures of the survivors. In their presentation of comparative survival data with literature reports or with chordoma, the authors do not address differences in survival related to other prognostic factors such as tumor size/extent of resection.

# Select Review in Neuro-Oncology

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

Volume: 1, Issue: 2

**Title:** CT and MR Imaging of focal calvarial lesions

**Review Type:** Article

**Category:** Neuro-Radiology

**Journal:** American Journal of Roentgenology, Vol: 172, No. 6: pages 1683-1688, June 1999

**Authors:** Arana E, Marti-Bonmati L

**Summary:** In a pictorial essay, the authors review the CT/MR characteristics in 165 biopsy-proven calvarial lesions (plus an additional 20 benign lesions that had a "classic" imaging appearance which did not change over time). They describe and present representative examples of the most common lesions they encountered including (in decreasing order of frequency): Langerhans histiocytosis, osteoma, epidermoid/dermoid cyst, metastases, meningioma, hemangioma, and fibrous dysplasia.

There is no discussion of "normal variants" such as venous channels ("venous lakes").

# Select Review in Neuro-Oncology

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

Volume: 1, Issue: 2

**Title:** Clinical Impact of MR Spectroscopy when MR imaging is indeterminate for pediatric brain tumors

**Review Type:** Article

**Category:** Neuro-Radiology

**Journal:** American Journal of Roentgenology, Vol: 173, No. 1: pages 119-125, July 1999

**Authors:** Norfray JF, Tomita T, Byrd SE, Ross BD, Berger PA, Miller RS

**Summary:** The authors obtained useful MR spectroscopic (MRS) data in 10/11 children (ages 3-14) with intracranial masses whose standard MRI study was considered "indeterminate" with respect to the nature of these lesions. Four patients had unknown masses that were being characterized, 2 patients with neurofibromatosis and basal ganglia masses were being evaluated for response to treatment, 1 patient with a chiasmatic glioma was being evaluated for response to treatment, patients with a meningioma and a pineoblastoma, respectively, were having the surgical beds evaluated for recurrent tumor, and 1 patient with a pontine glioma was having a follow-up evaluation to assess for possible radiation necrosis.

The single voxel proton MR spectra were obtained using a 1-7 cc voxel size, a scan time of approximately 10 minutes and normal-appearing contralateral brain as a control. Clinical management (e.g. to begin or withhold additional radiation therapy) was affected in the 10 patients in which MR spectra was successfully obtained. Four patients had histologic proof; the other six patients had clinical confirmation of the spectroscopic diagnosis based on their respective clinical courses including follow-up imaging and MRS up to 4 years later.

Interpretation of spectra was based on previous work. Findings were considered abnormal if they differed from the contralateral side (normal control) by > 10%.

Spectral findings:

Choline: increased in tumor progression, decreased in tumor regression, absent in radiation necrosis and gliosis, low or normal in benign masses

N-acetyl aspartate (NAA): decreased in tumor, decreases with tumor progression, low or normal in benign tumors, absent with radiation necrosis, stable with tumor regression, absent/low with scarring/gliosis, absent in non-neuronal tumors

Myo-inositol: elevated in tumors, absent in radiation necrosis

Creatine and lactic acid: less specific

The authors have confirmed earlier work (performed primarily in adults) that, in the setting of equivocal contrast-enhanced MRI findings (recurrent tumor vs. post-therapeutic gliosis/scarring or radiation necrosis), "neurochemical MR spectroscopic biopsy" may be able to replace a standard neurosurgical biopsy to determine pediatric brain tumor management in some patients.

Comment: More work needs to be done to determine the sensitivity and specificity of this technique. For example, if the wrong voxel of a suspicious area is evaluated, recurrent tumor could be missed. Similarly, small areas of recurrent tumor could be "averaged" with more normal surrounding brain and missed. Finally, the exact metabolite ratios (with the presumably normal contralateral "control" brain) that would define "abnormality" still need to be determined.

# Select Review in Neuro-Oncology

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

Volume: 1, Issue: 2

**Title:** Brain tumors: Complications of cerebral angiography accompanied by intra-arterial chemotherapy

**Review Type:** Article

**Category:** Neuro-Radiology

**Journal:** Radiology, Vol: 213, No. 1: pages 135-140, Oct 1999

**Authors:** Gelman M, Chakares DW, Newton HB

**Summary:** 48 patients (28 between the ages of 21 and 50; 20 above age 50) with primary (33) or secondary (15) intra-axial neoplasms underwent 392 consecutive intra-arterial catheterizations of either the internal carotid (228) or vertebral (164) arteries for the purpose of delivering a chemotherapeutic agent. Up to 24 infusions were made per patient. 5 Fr catheters were used and a low dose heparin flush was maintained during catheterization. Following a diagnostic angiogram, a 15 minute infusion of the chemotherapeutic agent (carboplatin or methotrexate) was performed followed by removal of the catheter.

Procedure-related complications included 10 groin hematomas, 2 catheter-related vasospasms, 2 catheter-related dissections, 5 minor systemic reactions (pain, bradycardia, headache) and 13 transient neurologic events (paresis, visual changes, seizures). No permanent neurologic deficits occurred.

This study confirms that intra-arterial chemotherapy can be safely given.

**Comment:** This study confirms that in experienced hands, intra-arterial catheterizations with infusion of chemotherapy can be safely performed. This study does not suggest whether or not there is any value to intra-arterial chemotherapy for the treatment of brain tumors (which remains a controversial therapy). Also, neurologic complication rates might be different with the use of different chemotherapeutic agents, different dosages of the agents used in this study or different catheterization techniques.

# Select Review in Neuro-Oncology

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

Volume: 1, Issue: 2

**Title:** Phases Ib and II multidose trial of gadolinium texaphyrin, a radiation sensitizer detectable at MR imaging: Preliminary results in brain metastases

**Review Type:** Article

**Category:** Neuro-Radiology

**Journal:** Radiology, Vol: 212, No. 3: pages 755-759, Sept 1999

**Authors:** Viala J, Vanel D, Meingan P, Lartigau E, Carde P, Renschler M

**Summary:** This study evaluates gadolinium texaphyrin, an experimental molecule which has shown promise as a radiation sensitizing agent (i.e. potentiates the effects of radiation therapy) in a mouse model.

This study reports the results of injection of this agent into 10 patients with known brain metastases treated with 2 week courses of 30 Gy fractionated (3 Gy/day) whole brain radiation therapy (RT) with the gadolinium texaphyrin administered intravenously each day immediately before the RT.

The dose of gadolinium texaphyrin (gad-tex) given to a patient group ranged from 0.25 micromol/kg to 4.10 micromol/kg. MR imaging was performed before initiation of RT, after the first dose of gad-tex (on the first day of RT), after the last dose of gad-tex (2 weeks after the initiation of RT) and 6 weeks after completing RT. 2 patients were also imaged 3-4 months after initiation of RT with one additional patient was imaged 6 and 9 months after initiation of RT.

The authors found that all dosages of the gadolinium texaphyrin were tolerated and that enhancement of metastases increased over the 2 week course of daily injections of the agent (followed by daily RT) suggesting accumulation of the agent within metastases. The agent resulted in enhancement of only presumed metastases and not normal brain. Enhancement persisted on delayed imaging including the 6 month and 9 month post-RT scans.

The authors found that gadolinium texaphyrin can be safely administered at the doses evaluated in this study and appears to accumulate within metastases and not in normal brain (i.e. it is tumor specific). As it appears to persist within lesions for months, response or lack of response to therapy can be evaluated without injection of an additional enhancing agent at follow-up MR scanning.

Comment: While gadolinium texaphyrin appears to be safe when given intravenously at the doses used in this study, and while it does appear to accumulate and remain within metastases (for at least 9 months when initially given at a dose of 1.3 micromol/kg), its radiation-sensitizing effects, if any, remain unknown.

# Select Review in Neuro-Oncology

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

Volume: 1, Issue: 2

**Title:** Necrotic tumor vs brain abscess: Importance of amino acids detected at H1 MR spectroscopy-Initial results

**Review Type:** Article

**Category:** Neuro-Radiology

**Journal:** Radiology, Vol: 213, No. 3: pages 785-793, Dec 1999

**Authors:** Grand S, Passaro G, Ziegler A et al

**Summary:** The authors performed an in vitro and in vivo study using proton MR spectroscopy (MRS) to search for amino acid resonances in an attempt to distinguish between cystic brain tumors and bacterial abscesses.

The authors found that the methyl groups from valine, leucine and isoleucine amino acids in cystic (necrotic) brain tumor specimens and in purulent brain tissue specimens could be detected in vitro using MRS and liquid chromatography. However, in this study, they also found that the amino acid concentrations detectable from in vitro cystic neoplasms were far below the detectable limits (using MRS) of such moieties present within in vivo cystic brain neoplasms.

Next, in 34 patients with cystic intracranial lesions (28 tumors, 6 abscesses), the authors found no overlap in the ranges of amino acid concentrations detectable in vivo with MRS. Specifically, a spectral peak at 0.9 ppm was only detectable in the abscess cases.

The authors conclude that MRS is a promising technique for distinguishing between cystic neoplasms and bacterial abscesses.

Comments: All lesions in this study were at least 2 cms in diameter. The potential value of this technique for smaller lesions is unknown.

This study evaluated only bacterial infections and therefore the technique would not necessarily be useful for identifying non-bacterial infections (which, for example, might be important when attempting to differentiate between toxoplasmosis and lymphoma).

None of these patients were HIV positive or were in any way immunocompromised, so it is unknown if bacterial infections in immunocompromised patients would demonstrate similar findings.

# Select Review in Neuro-Oncology

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

Volume: 1, Issue: 2

**Title:** Late radiation injury to the temporal lobes: Morphologic evaluation at MR imaging

**Review Type:** Article

**Category:** Neuro-Radiology

**Journal:** Radiology, Vol: 213, No. 3: pages 800-807, Dec 1999

**Authors:** Chan Y-I, Leung S-f, King AD, Choi PHK, Metreweli C.

**Summary:** The authors reviewed the MR appearance of "late" radiation change in 68 temporal lobes in 34 patients treated for nasopharyngeal carcinoma with radiation therapy (66-71 Gy target volume dose) between 2 and 10 years earlier.

The authors found changes in 57/68 temporal lobes with a wider range of imaging findings than those usually attributed to chronic radiation change. Observed findings included the typical high signal white matter changes on T2-weighted scans, but also areas of heterogeneous signal consistent with necrosis, gray matter signal abnormalities, areas of presumed hemosiderin deposition and areas of blood-brain-barrier breakdown (i.e. pathologic contrast enhancement).

While no histologic proof was obtained in this study, direct intracranial extension by recurrent nasopharyngeal carcinoma is unusual and it is fair to conclude that the observed temporal lobe abnormalities are due to radiation effects.

The authors conclude that there is a wide range of gray and white matter findings that may be seen years after radiation therapy that are due to the radiation and should not automatically suggest another more aggressive underlying intra-axial process.

Comment: In the setting of an intra-axial neoplasm treated years previously (at least 2 years earlier) by radiation therapy, such dramatic changes as those demonstrated in this study are usually attributed to recurrent neoplasm. However, the authors findings should at least suggest the possibility of radiation-related injury instead of recurrent neoplasm.

However, note is also made that the author's findings in this study can only be directly correlated to radiation therapy given as treatment for nasopharyngeal carcinoma and cannot necessarily be extrapolated to radiation therapy given for intra-axial neoplasms.

# Select Review in Neuro-Oncology

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

Volume: 1, Issue: 2

**Title:** Intraoperative MR Imaging Increases the Extent of Tumor Resection in Patients with High-Grade Gliomas

**Review Type:** Article

**Category:** Neuro-Radiology

**Journal:** Am J Neuroradiol, Vol: 20, No. : pages 1642-1646, Oct 1999

**Authors:** Knauth M, Wirtz CR, Tronnier VM, et al.

**Summary:** This study was designed to assess the hypothesis that intraoperative MR imaging improves surgical results in patients with high-grade gliomas. 38 patients underwent surgery for high-grade gliomas using a stereotactic neuronavigation system. A total of 41 procedures were performed in this group. After the neurosurgeon felt he had removed all enhancing tissue using neuronavigation and would have stopped the procedure, intraoperative MR was obtained using a 0.2T MR system. If necessary and feasible, surgery was continued to remove remaining enhancing tissue.

Intraoperative MR showed residual enhancing abnormality in 54% of cases, none in 37%, and inconclusive results in 9%. Surgery was continued in 17 of 22 cases with residual enhancement. Fourteen of these cases subsequently showed no enhancement on postoperative standard MR imaging.

This study is a first step in proving efficacy for intraoperative MR in guiding surgical treatment of high-grade gliomas. However, this study does not assess the impact of this expensive technology on patient outcome, and further studies will be needed to evaluate this endpoint.

# Select Review in Neuro-Oncology

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

Volume: 1, Issue: 2

**Title:** Quality of life in patients with stable disease after surgery, radiotherapy and chemotherapy for malignant brain tumor.

**Review Type:** Article

**Category:** Neurology

**Journal:** Journal of Neurology, Neurosurgery and Psychiatry, Vol: 67, No. 3: pages 358-63, Sep. 1999

**Authors:** Giovagnoli, AR

**Summary:** Successful treatment for central nervous system neoplasms should prolong life and enhance quality of life. This study enrolled fifty seven patients with malignant intrinsic brain tumors with stable disease after completing a treatment regimen consisting of surgery, whole brain radiotherapy and chemotherapy. Subjects were investigated using a variety of indices including Karnofsky performance, cognitive testing and a self-rating depression scale. A control group of patients with non-neoplastic chronic neurologic disorders (e.g. multiple sclerosis, myasthenia gravis, spastic paraparesis, etc.) was similarly evaluated. Important comparisons included return to work (73% in tumor patients, 58% controls). The Functional Living Index-Cancer, a health related quality of life index developed for non-central nervous system malignancies, was slightly higher for this study than for published systemic cancer series.

The author concedes that this is a highly selected population. The patients enrolled all started with Karnofsky scores >60 and glioblastomas were underrepresented. Nevertheless, the data suggest that patients aggressively treated for malignant brain tumors have equal, and perhaps better, quality of lives compared to cohorts of patients with other chronic central nervous system diseases.

# Select Review in Neuro-Oncology

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

Volume: 1, Issue: 2

**Title:** Which Glioblastoma Multiforme Patient will Become a Long-Term Survivor? A Population-Based Study

**Review Type:** Article

**Category:** Neurology

**Journal:** Annals of Neurology, Vol: 46, No. 2: pages 183-188, Aug 99

**Authors:** Scott JN, Rewcastle NB, et al

**Summary:** The average prognosis for patients harboring glioblastoma multiforme (GBM) remains grim but the exceptional case of survival for many years is well known. The authors attempt to explore the factors contributing to long term survival in this case controlled population based study. The Alberta Cancer Registry was used to identify all patients with GBM surviving beyond three years. Only 2.2% of all GBM patients were long term survivors (LTS) after histologic review. Of the factors investigated the following reached significance when comparing LTS to the total cohort of GBM patients: LTS were much more likely to have undergone gross total tumor resection, had higher Karnofsky scores at presentation and were more likely to have undergone treatment with chemotherapy.

Histologically, LTS patients had lower mitotic indices as measured by Ki-67 immunostaining. Nearly half of the LTS specimens were revised from the original diagnosis of GBM after histologic review. The authors note that treatment recommendations cannot be made from this type of analysis but as a population based study it provides more representative data than previous hospital based series.

# Select Review in Neuro-Oncology

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

Volume: 1, Issue: 2

**Title:** Management of Intrinsic Gliomas of the Tectal Plate in Children

**Review Type:** Article

**Category:** Pediatrics/Pediatric Neuro-Oncology

**Journal:** Pediatric Neurosurgery, Vol: 31, No. 4: pages 170-176, October 1999

**Authors:** Grant GA, Avellino AM, Loeser JD, Ellenbogen RG, Berger MS, and Roberts TS

**Summary:** The authors performed a 10 year, retrospective, institutional review of pediatric patients with intrinsic tectal plate gliomas. Eleven consecutive patients (7 F, 4 M) were followed for an average of 5 years after diagnosis by serial neurological examination, CT and MR imaging. The majority of the patients presented with headache (91%), papilledema (82%) or other signs of intracranial hypertension. One (9%) had Parinaud's syndrome. All eleven patients underwent CSF diversion procedures (VP shunt or IIIrd ventriculostomy): 10 patients at presentation and one patient two years later. No patient underwent biopsy or resection. In three patients, the lesion (based on MR T2 hyperintensity) was greater than 1.5 cm in diameter and, in three patients, small areas of gadolinium enhancement were present. Three patients with either one or both of these features showed asymptomatic, subtle radiological progression. No patient without either of these features showed radiological or clinical progression. The authors conclude that CSF diversion without biopsy or resection, followed by radiological surveillance, is appropriate management of intrinsic tectal plate gliomas in children, particularly those that are small (< 1.5 cm) and show no contrast enhancement.

# Select Review in Neuro-Oncology

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

Volume: 1, Issue: 2

**Title:** Improved Survival of Children with Isolated CNS Relapse of Acute Lymphoblastic Leukemia: A Pediatric Oncology Group Study

**Review Type:** Article

**Category:** Pediatrics/Pediatric Neuro-Oncology

**Journal:** Journal of Clinical Oncology, Vol: Vol 17, No. 12: pages 3745-52, Dec. 1999

**Authors:** Ritchey AK, Pollock BH, Lauer SJ, et al

**Summary:** The outlook for children with acute lymphoblastic leukemia (ALL) who sustain a meningeal relapse has been poor. Eighty-three patients (pts) with ALL in first bone marrow remission who experienced an isolated CNS relapse were treated with induction (4 weeks [wks]), consolidation (6 wks), and intensification (12 weeks) intravenous (IV) and intrathecal (IT) chemotherapy followed by craniospinal irradiation (CSI) (24 Gy cranial/15 Gy spinal), and then 85 weeks of maintenance chemotherapy. Provision of radiotherapy (RT) was delayed because the ability to deliver intensive chemotherapy is compromised by poor marrow reserve (after CSI). Forty-eight of these pts were classified as standard risk and 35 as high risk using previously described parameters.

All 83 patients achieved a central nervous system (CNS) remission after induction chemotherapy. Cox regression analysis was used to estimate the association between event free survival (EFS) and multiple clinical variables. The only significant prognostic factor was the length of the initial remission. The 4-year cumulative EFS rate for pts with first remission of  $\geq 18$  months was 83.3%  $\pm$  5.3%, and for pts with a first remission  $<18$  months it was 46.2%  $\pm$  10.2%. Only 6 patients experienced significant neurologic symptoms during treatment although there was an unexpectedly high rate of severe (not fatal) reactions to L-asparaginase. Twenty-eight patients were removed from the study because of relapse (n=14), toxicity (n=5), secondary malignancy (n=5), bone marrow transplantation in remission (n=3), or because they were lost to follow-up (n=1).

Studies of children with CNS relapse of ALL treated in the 1970's and early 1980's described continuous complete remission rates of 10-60% with most reporting 25-50% - most of these failures had occurred in the bone marrow. Although there were two patients with reported relapses before radiation in the present study, the 6 month delay otherwise afforded more appropriate bone marrow coverage, preventing recurrence in a substantial proportion of the remaining patients. This study marks a significant advancement in the treatment of ALL with CNS relapse demonstrating a 4 year EFS similar to that of patients who with newly diagnosed and no CNS involvement. Spin-off studies will look to improve EFS in the newly described high risk group (first remission  $<18$  months) with further dose intensification and 12 month RT delay. Also, there will be attempts to limit RT toxicity / total dosage in the low-risk group.

# Select Review in Neuro-Oncology

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

Volume: 1, Issue: 2

**Title:** A Phase 3 Randomized Study of Radiotherapy Plus PCV With or Without BUdr for the Treatment of Anaplastic Astrocytoma: A Preliminary Report of RTOG 9404

**Review Type:** Article

**Category:** Radiation Oncology

**Journal:** International Journal of Radiation Biology Physics, Vol: 45, No. 5: pages 1109-1115, Dec. 1999

**Authors:** Prados MD, Scott C, et al

**Summary:** BUdr is a halogenated pyrimidine which is substituted for thymidine in the DNA of actively dividing cells and has been shown in-vitro in glioma cell lines to be a radiosensitizer. In 1991 UCSF began a phase III randomized trial comparing the addition of BUdr(or IUdr) to RT/PCV in the postoperative treatment of anaplastic astrocytoma. In 1994 RTOG, SWOG, and NCCTG joined the study, making it an intergroup trial. As of 1997, 281 of planned 293 patients were enrolled and the study was closed based on an interim analysis which showed no survival advantage with BUdr( 1 year survival estimate of 68% with BUdr vs. 82% without,  $p=0.96$ ; it is unclear why there were more deaths in the BUdr arm). A final report will be issued in three years, but the outcome with longer followup is not anticipated to be any different.

As pointed out in the article, 30% of enrolled patients were excluded from analysis, many on the basis of discordant pathology review, again highlighting the interobserver variability in the pathologic diagnosis of AAF. The negative results with BUdr will be undoubtedly be disappointing to many investigators(especially since the Phase II NCOG data had looked encouraging), but again confirm the importance of a phase III trial.

**References:** Accompanying editorial by WKA Yung.

# Select Review in Neuro-Oncology

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

Volume: 1, Issue: 2

**Title:** Pretreatment factors predict overall survival for patients with low-grade glioma: a recursive partitioning analysis

**Review Type:** Article

**Category:** Radiation Oncology

**Journal:** IJROBP, Vol: 45, No. 4: pages 923-929, 1999

**Authors:** Bauman G, Lote K, Larson D, et al.

**Summary:** Dr. Bauman and colleagues have presented a very large compilation of low-grade gliomas treated at 3 centers (UCSF in the US, NRH in Norway and the LRCC in London, England). The data was analyzed to develop a model to predict outcome in this patient population. 401 patients 18 years or older were analyzed. The institutions had similar patient characteristics except at LRCC 49% had >90% resection compared to 13% and 17% at UCSF and NRH respectively. In addition, the Oligodendroglioma/mixed category was 44%, 23%, and 79% and the "delayed radiotherapy" was 50%, 0%, 11% at LRCC, UCSF, and NRH respectively. These differences make interpretation of the data with regards to outcome by institution difficult but none the less, a stratified prognostic factor grouping was successfully developed.

Overall survival on univariate and multivariate analysis was better at UCSF than at LRCC, and NRH. In addition, age (18-40), seizures at presentation, KPS>70 and no contrast enhancement independently predicted for increased survival.

A Recursive partitioning analysis was then accomplished, however the treating institution was not included in the modeling. This analysis found 4 groups of patients with different prognoses. Group I: KPS<70, age>40 had median survival (MS) of 12 months. Group II: KPS >69, age >40 with enhancement experienced an MS of 46 months. Group III: KPS<70, age 18-40, or KPS>69 and age >40 with no enhancement, experienced a MS of 87 months. Finally Group IV: KPS>69, and age 18-40 experienced a MS of 128 months.

A thorough discussion of recent randomized trials and their available data was then discussed. Given the high likelihood that at UCSF MRI data was routinely used for treatment planning, it is not surprising that their patients may have done better for this reason. However, I am not aware of the imaging type used for treatment planning at LRCC and at NRH so this is entirely speculative on my part.

In the EORTC study IJROBP 36(3):549-556, 1996, planning did not require MRI and "minimal margin" was used for the boost in the high dose arm. In the NCCTG study published by Shaw et al. in abstract form, comparing 5040cGy to 6480cGy, MRI was suggested but not mandated for treatment planning as this study was designed in the late 80's. Of note, on that study, of the 62 patients entered by Mayo, 18 had treatment planning done by CT and all but one were treated before 1991.

Overall survival in the EORTC trial was no different between 45 and 59.4Gy, which means as we take the brain to tolerance with EBRT, we still have approximately 50% progression at 5 years and survival with a very similar curve in these "benign" tumors. This may be due to lack of MRI treatment planning or due to the inability to cure these tumors at 45 or 50.4Gy, or even 59.4Gy as mentioned above. The OS and PFS from the NCCTG dose comparison study is not yet available, but Shaw has reported a difference in toxicity with 4% brain necrosis at 64.8Gy and 2% at 50.4 Gy.

In summary this data set helps the clinician further define prognostic factors in low-grade glioma patients

# Select Review in Neuro-Oncology

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

Volume: 1, Issue: 2

**Title:** Surgery and Radiotherapy compared to gamma knife radiosurgery in the treatment of solitary cerebral metastases of small diameter

**Review Type:** Article

**Category:** Radiation Oncology

**Journal:** Journal of Neurosurgery, Vol: 91, No. : pages 35-43, July 1999

**Authors:** Muacevic A, Kreth FW, Horstmann GA, Schmid-Elsaesser R, Wowra B, Steiger HJ, Reulen HJ

**Summary:** This article reports a retrospective comparison from Germany of gamma knife radiosurgery alone versus microsurgical excision and whole brain radiation therapy (WBRT) in the management of "solitary" metastases. 52 patients treated with surgery and WBRT (50 Gy) were selected for comparison who met the criteria for radiosurgery: size less 3.5 cm, single met on MRI scan, stable systemic disease, and not requiring surgical decompression. These were then compared to 56 patients treated at the Munich Gamma Knife Center with radiosurgery alone followed by radiosurgery alone for salvage. Local control between the two modalities were equivalent at 75% for S+WBRT versus 83% for RS. The S+WBRT arm did have a better one year freedom from distant brain recurrence (68% vs. 90%) but all of the RS arm treated distant brain failures were successfully salvaged. The neurologic death rate was similar at 37% vs. 39%. There was a nonsignificant survival difference of 10% at one year favoring the surgical arm due to slower progression of systemic disease.

This article provides important guidance in the management of single brain metastasis patients. Radiosurgery alone without the time, expense, and neurocognitive sequelae of WBRT is a feasible strategy for patients with stable extracranial disease. MRI surveillance is necessary to identify and salvage distant brain recurrences. The radiosurgery local control results are equivalent to those of surgery and WBRT in contrast to the poor local control seen for surgery alone in the randomized trial by Patchell. et al. In the absence of a randomized trial, this paper adds to the preponderance of data supporting the clinical equivalence of radiosurgery to surgical resection for a single brain metastasis. As radiosurgery is less invasive and WBRT can be avoided, it would seem to be a preferable strategy.

**Note:** The title is a misnomer as "solitary brain met" refers to the absence of extracranial disease. The appropriate term is "single brain met".

# Select Review in Neuro-Oncology

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

Volume: 1, Issue: 2

**Title:** Stereotactic radiosurgery plus whole brain radiotherapy versus radiotherapy alone for patients with multiple brain metastases

**Review Type:** Article

**Category:** Radiation Oncology

**Journal:** Int J Radiat Oncol Biol Phys, Vol: 45, No. 2: pages 427-434, 1999

**Authors:** Kondziolka D; Patel A; Lunsford LD; Kassam A; Flickinger JC

**Summary:** This important study from the University of Pittsburgh program evaluated whether radiosurgery plus Whole Brain Radiation Therapy (WBRT) would provide improved local brain tumor control over WBRT alone in patients with two to four brain metastases. Patients were randomized to initial brain tumor management with WBRT alone (30 Gy in 12 fractions) or WBRT plus radiosurgery (16 Gy). Twenty-seven patients were randomized (14 to WBRT alone and 13 to WBRT plus radiosurgery). The rate of local failure at 1 year was 100% after WBRT alone but only 8% in patients who had boost radiosurgery. The median time to local failure was 6 months after WBRT in comparison to 36 months after WBRT plus radiosurgery ( $p = 0.0005$ ). Patients who received WBRT alone lived a median of 7.5 months, while those who received WBRT plus radiosurgery lived 11 months ( $p = 0.22$ ).

This article provides very important randomized data establishing the worth of SRS in the management of patients with 2-4 brain metastases minimally selected for extent of systemic disease. The local control and survival differences are striking although there are a few caveats. It is puzzling why the randomization was stopped after only 27 patients based on an intermediate marker like local control. In cancer patients, dramatic differences in local control do not always justify an aggressive treatment. Despite the local control benefit, not enough patients were accrued to establish a significant survival advantage although the absolute difference was impressive (11 months vs. 7.5 months). Another fault of this study is that it used a suboptimal dose of WBRT in the control arm for relatively good prognosis patients (30 Gy in 12 fx) thus exaggerating the local control difference. At 2.5 Gy per fraction most U.S. institutions would use 35 or 37.5 Gy. 30 Gy in 12 fractions is an appropriate dose for control of subclinical disease when given in conjunction with RS. In spite of these problems, the paper does establish a rationale for using radiosurgery for two to four brain metastases in favorable patients with extracranial disease. Moderate dose WBRT for these patients is simply inadequate and well tolerated radiosurgical treatment can markedly delay the time to neurological failure and possibly death.

# Select Review in Neuro-Oncology

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

Volume: 1, Issue: 2

**Title:** Prophylactic Cranial Irradiation in Locally Advanced Non-Small-Cell Lung Cancer After Multimodality Treatment: Long Term Follow-Up and Investigations of Late Neuropsychologic Effects

**Review Type:** Article

**Category:** Radiation Oncology

**Journal:** Journal of Clinical Oncology, Vol: 17, No. 9: pages 2700-2709, Sept. 1999

**Authors:** Stuschke M, Eberhardt W, Pottgen C, Stamatis G, Wilke J, Stuben H, et al

**Summary:** This fascinating report from the Ruhrländlinik in Germany details their results from utilizing prophylactic cranial irradiation (PCI) in a preoperative chemoradiation trial for locally advanced (Stages IIIA, IIIB) non-small cell lung cancer. PCI (30 Gy in 15 fractions) was routinely offered to patients midway through accrual of 75 patients in this Phase II trial. PCI reduced the incidence of brain metastasis as the first site of relapse from 30% to 8% and the overall brain relapse rate from 54% to 13%. PCI reduced the relative risk of death by 50% on multivariate analysis ( $p < 0.05$ ). Careful neuropsychologic testing on long term survivors revealed similar impairments in attention and visual memory regardless of PCI. The PCI group did have greater T2 white matter changes on MRI which were not clinically significant.

This study adds to the body of literature which suggests that non-small cell subclinical brain mets are just as sensitive as small cell. A well tolerated modest dose of radiation can prevent a high rate of brain metastases and probably improve survival rates. As therapy for lung cancer intensifies, it is essential to maximize the chance of cure by eliminating the brain as a sanctuary site for disease. Based on the Arriagada randomized data and this trial, we can probably safely say that PCI at less than 30 Gy in 15 fractions to the brain will not lead to untoward neuropsychologic effects. In addition, this study did not find increasing cognitive effects of PCI with age. We need a randomized trial in the US to determine whether there is a survival advantage for PCI in favorable patients treated with current aggressive therapies.

# Select Review in Neuro-Oncology

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

Volume: 1, Issue: 2

**Title:** Noninvasive Differentiation of Progressive Brain Tumor from Radiation Injury after Stereotactic Radiotherapy by Using Proton MR Spectroscopy

**Review Type:** Meeting Abstract

**Category:** Neuro-Radiology

**Meeting:** Radiological Society of North America, November 28-December 3, 1999

**Summary:** **PURPOSE:** To evaluate the clinical utility of proton MR spectroscopy (1H-MRS) in a combined MRI/1H-MRS examination protocol for differentiating progressive tumor from radiation injury.

**METHOD AND MATERIALS:** In this ongoing study 110 MRI/1H-MRS examination have been performed up to now in 62 patients treated by stereotactic radiotherapy for grades II, III and IV gliomas. The MRI protocol included multiplanar T2-w turbo spin-echo as well as pre- and postcontrast T1-w spin-echo images. 1H-MR spectra (PRESS, TR=1500 ms, TE =135 ms) were obtained before contrast-medium administration. Voxels (size: 1 to 12 ml) were centered in one or more suspected lesions and in 45 patients also in contralateral control regions. Spectra were evaluated by using a LPSVD algorithm in the time domain and relative signal intensities of choline (Cho), total creatine (CR) and N-acetyl-aspartate (NAA), lactate, and free lipids were calculated. Diagnoses were established on clinical and follow-up MRI examinations, PET or SPECT studies or biopsy.

**RESULTS:** Significantly higher signal intensity ratios of Cho/Cr ( $p < 0.0001$ ) were found in lesions related to progressive or recurrent disease (PD) as compared to lesions classified as stable disease (SD) ( $p < 0.0001$ ) and lesions related to radiation injury (RI) (edema, gliosis, contrast enhancement, radiation necrosis;  $p < 0.0001$ ). No differentiation between SD- and RI-lesions was possible. For Cho/Cr values between 1.5 and 2.5 a discrimination of PT-, SD- and RI-lesions was not possible. In patients with RI-lesions, however, follow-up examinations revealed a decrease or no change of Cho/Cr-values. Large interindividual variations in progressive tumors may probably indicate different tumor histologies. Radiation necrosis was associated with release and hence MR-detectability of free lipids and could be differentiated from high grade gliomas by relatively low Cho/Cr.

**CONCLUSIONS:** 1H-MRS is a useful and practicable tool for evaluating suspicious brain lesions after radiotherapy of glial brain tumors. In view of the differential diagnosis between progressive or recurrent brain tumor and radiation-related tissue alterations it has the potential to increase the accuracy of MRI. Furthermore, the approach of a combined MRI/1H-MRS follow-up examination protocol may reduce the number or avoid additional diagnostic procedures, e.g. PET-scanning, and may consequently reduce the costs of the diagnostic follow-up protocol.

# Select Review in Neuro-Oncology

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

Volume: 1, Issue: 2

**Title:** Neuroradiology Keynote Speaker: The Time Course of Blood Brain Barrier (BBB) Closure after Hyperosmotic Disruption (HD) in Patients with Brain Tumors

**Review Type:** Meeting Abstract

**Category:** Neuro-Radiology

**Meeting:** Radiological Society of North America, November 28-December 3, 1999

**Summary:** **PURPOSE:** To assess in-vivo the time course of BBB closure following HD produced by intra-arterial infusion of mannitol in conjunction with chemotherapy for the treatment of brain tumors in humans. Animal studies show closure of the BBB by 30 minutes. The only human study showed closure by 10 minutes.

**METHOD AND MATERIALS:** Disruption of the BBB was demonstrated by Tc-99m glucoheptonate (TcGH) SPECT scanning in 10 pts treated monthly with combination chemotherapy in conjunction with HD. Primary diagnoses were: CNS lymphoma (n=6) and PNET (n=4). TcGH (20 mCi) was injected intravenously at 1-480 minute intervals after HD and patients were scanned 4 hours later. 36 studies were performed.

**RESULTS:** TcGH indices one minute post HD correlated well with the degree of barrier disruption measured on post procedure contrast enhanced CT scans ( $r=0.852$ ). The TcGH indices for patients with good disruption were 2.19  $\pm$  0.18 at 1 minute, 2.13  $\pm$  0.20 at 40 minutes, 1.53  $\pm$  0.09 at 90 minutes, 1.36  $\pm$  0.02 at 120 minutes, and back to baseline value of 1.00 at 480 minutes after disruption. For patients with poor disruption the TcGH indices were 1.55  $\pm$  0.10 at 1 minute and back to baseline by 120 minutes.

**CONCLUSIONS:** This in-vivo human study suggests that the time course of closure of the disrupted BBB is significantly longer than previously estimated. The BBB closure appears to follow three phases: 1) A constant fully open BBB for the initial 40 minutes. 2) A rapid linear decline to about a quarter of the initial opening over the next 80 minutes. 3) A gradual linear decline for another 360 minutes. This longer time window of BBB opening has implications for the optimal time course of chemotherapy infusion. It also indicates that the brain is exposed to toxins, that don't cross the normally intact BBB, for a much longer period than initially thought.

# Select Review in Neuro-Oncology

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

Volume: 1, Issue: 2

**Title:** The Role of Contrast-enhanced Perfusion MR Imaging in Differentiating between Recurrent Brain Tumor and Radiation Necrosis

**Review Type:** Meeting Abstract

**Category:** Neuro-Radiology

**Meeting:** Radiological Society of North America, November 28-December 3, 1999

**Summary:** **PURPOSE:** Dynamic contrast enhanced (perfusion-weighted) MR imaging provides information on the location and degree of neovascularization in the brain. The purpose of our study was to evaluate the role of contrast enhanced perfusion-weighted MR imaging in differentiating between recurrent brain tumor and post-therapy radiation necrosis.

**METHOD AND MATERIALS:** Conventional and perfusion MR images, histopathological findings, and medical records of 35 consecutive patients with a history of a treated intracranial neoplasm were evaluated retrospectively. All patients had received radiation treatment, including high-dose external beam radiation or radiosurgery. Follow up imaging studies were performed because of clinical suspicion of recurrent tumor or radiation necrosis. Conventional MR imaging findings and MR measurements of relative cerebral blood volume (rCBV) of the lesion were evaluated. All 35 patients underwent repeat biopsy or resection.

**RESULTS:** MR perfusion imaging findings were confirmed histologically in all 35 patients. With contralateral white matter as the standard of comparison, the MR perfusion of the lesion was considered hyperperfusing when rCBV was greater than 1. Tumor was found histologically in all 30 patients demonstrating an area of hyperperfusion within the lesion. In the remaining 5 patients who showed no area of increased rCBV, the lesion was found to be post-therapy radiation necrosis with no evidence of tumor.

**CONCLUSIONS:** Our data suggest that contrast enhanced perfusion MR imaging may accurately differentiate recurrent tumor from radiation necrosis.

# Select Review in Neuro-Oncology

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

## What's Hot in Neuro-Oncology

Volume: 1, Issue: 2

**Title:** Controversial Issues in the Management of Brain Metastases

**Category:** Adult Neurosurgery

**Contributor(s):** Edward Shaw, MD

**Institution:** Wake Forest University School of Medicine

**Summary:** For three decades, the standard management of patients with multiple brain metastases has been whole brain radiation therapy (WBRT), usually 3000 cGy in 10 fractions. The results are quite predictable: median survival is about 4 months, and while half of patients will improve neurologically within 1-3 weeks, half will develop progressive neurologic symptoms within 8-12 weeks, and half will die because of uncontrolled brain metastases. Surprising? No. Predictable? Yes. Fletcher's basic principles of radiotherapy have told us for years that even minimal (1-2 cm) gross disease requires >7000 cGy to achieve >90% local control. Certainly, such doses cannot be achieved with WBRT. For patients with a limited number of metastases (< 3 or 4), a logical approach to the problem includes the use of stereotactic radiosurgery (SRS) as a means of "boosting" dose to the gross disease. While one can criticize the University of Pittsburgh randomized trial of WBRT +/- SRS boost for patients with 2-4 small (<25 mm) brain metastases for having an inadequate sample size and therefore not being a "definitive" study, one can hardly ignore the dramatic difference in the one-year local control rate (100% with WBRT + SRS versus 8% with WBRT alone). The similarity in survival (11 months) between patients who had WBRT + SRS up-front or WBRT with SRS at the time of local failure suggests that radiosurgical salvage of WBRT failures is still a very reasonable practice option for these patients. Within the next year, results of the large RTOG 9508 clinical trial should be available, in which patients with 1-3 small to moderate sized brain metastases (<40 mm) were randomized to receive WBRT +/- SRS. Approximately 400 patients were accrued. As a successor trial, the RTOG is considering a randomization of the same patient population to SRS +/- WBRT. Is such a study reasonable to consider? The answer is yes. Half of patients with metastatic disease to the brain will have a solitary lesion, another 15% will have two lesions, and 10% will have three over the natural history of their malignancy. This would imply that 75% of patients with brain metastases could (should?) be managed effectively by local means (surgery, SRS) rather than "mandatory" WBRT. The European Organization for the Research and Treatment of Cancer has an ongoing study addressing this issue: patients with a solitary metastasis undergo surgery and SRS followed by randomization to observation or WBRT, while those with several metastases undergo SRS followed by the same randomization. It is said that the only thing harder than getting an old idea out of someone's head is getting a new one in. Suffice it to say that we must challenge ourselves to seek and find more effective ways to treat patients with brain metastases ... especially since the incidence of this neurologic complication of cancer (nearly 200,000 cases per year) is approaching that of common solid tumors like lung, breast, and prostate cancer.

**References:** Shaw EG: Radiotherapeutic management of multiple brain metastases: "3000 in 10" whole brain radiation is no longer a "no brainer". *Int. J. Radiation Oncology Biol. Phys.* 45:253-254, 1999.

# Select Review in Neuro-Oncology

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

## Featured Article

Volume: 1, Issue: 2

**Title:** Stereotactic radiosurgery plus whole brain radiotherapy versus radiotherapy alone for patients with multiple brain metastases

**Category:** Adult Neurosurgery

**Journal:** International Journal of Radiation Oncology, Biology, and Physics, Vol: 45, No. : pages 427-434, 1999

**Authors:** Kondziolka D, Patel A, Lunsford LD, Kassam A, Flickinger JC.

**Summary:** Multiple brain metastases are a common health problem, frequently diagnosed in patients with cancer. The prognosis, even after treatment with whole brain radiation therapy (WBRT), is poor with average expected survivals less than six months. Retrospective series of stereotactic radiosurgery have shown local control and survival benefits in case series of patients with solitary brain metastases. We hypothesized that radiosurgery plus WBRT would provide improved local brain tumor control over WBRT alone in patients with two to four brain metastases.

Patients with two to four brain metastases (all < 25 mm diameter and known primary tumor type) were randomized to initial brain tumor management with WBRT alone (30 Gy in 12 fractions) or WBRT plus radiosurgery. Extent of extracranial cancer, tumor diameters on MRI scan, and functional status were recorded before and after initial care. The study was stopped at an interim evaluation at 60% accrual. Twenty-seven patients were randomized (14 to WBRT alone and 13 to WBRT plus radiosurgery). The groups were well matched to age, sex, tumor type, number of tumors, and extent of extracranial disease. The rate of local failure at one year was 100% after WBRT alone but only 8% in patients who had boost radiosurgery. The median time to local failure was 6 months after WBRT alone (95% C.I., 3.5-8.5) in comparison to 36 months (95% C.I., 15.6-57) after WBRT plus radiosurgery ( $p=0.0005$ ). The median time to any brain failure was improved in the radiosurgery group ( $p=0.002$ ). Tumor control did not depend on histology ( $p=0.85$ ), number of initial brain metastases ( $p=0.25$ ), or extent of extracranial disease ( $p=0.26$ ). Patients who received WBRT alone lived a median of 7.5 months, while those that received WBRT plus radiosurgery lived 11 months ( $p=0.22$ ). Survival did not depend on histology or number of tumors, but was related to extent of extracranial disease ( $p=0.02$ ). There was no neurologic or systemic morbidity related to stereotactic radiosurgery.

Thus, combined whole brain radiation therapy and radiosurgery for patients with two to four brain metastases significantly improved control of brain disease. Whole brain radiation therapy alone did not provide lasting and effective care for most patients.

This report was the first randomized trial for patients with multiple metastases. Its limitations include a relatively small number of patients, the inclusion of all histologic tumor types, and the lack of information regarding functional outcomes. The primary outcome was imaging-defined tumor control, which was improved in the patients who received radiosurgery. We now recommend that all patients in reasonable functional condition consider radiosurgery in addition to WBRT if they harbor 2-4 brain tumors. WBRT alone does not appear to be a robust treatment strategy and may cause adverse effects, although it may provide some benefit in reducing the incidence of new metastases. We plan to test the effectiveness of WBRT in a second randomized trial.