



SELECT REVIEW IN NEURO-ONCOLOGY



Editor-in-Chief
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Charlotte, North Carolina



American
Association of
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Surgeons

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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 with any questions or comments.

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Radiation Oncology

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Journal: *Proceedings of ASTRO (International Journal of Radiation Oncology Biology Physics)*, Vol: 48, No. 3 (supplement): pages 113-114, October, 2000

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What's Hot in Neuro-Oncology

Adult Neurosurgery

Title: Proxima Therapeutics' Gliasite Radiation Therapy System: Newly FDA Approved for Malignant Brain Tumors

Contributors: Steven B. Tatter, M.D., Ph.D.

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Select Review in Neuro-Oncology

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

Volume: 2, Issue: 2

Title: Adult Medulloblastoma: prognostic factors and patterns of relapse

Review Type: Article

Category: Adult Neurosurgery

Journal: Neurosurgery, Vol: 47, No. : pages 623-632, Sept. 2000

Authors: Chan AW, Tarbell NJ, Black PM, Louis DN, Frosch MP, Ancukiewicz M, Chapman P, Loeffler JS

Summary: Adult medulloblastomas (MBs) are rare neoplasms, and data regarding prognostic factors and patterns of relapse in these patients are sparse in the neurosurgical literature. This group of investigators from Harvard have carried out a retrospective analysis of 32 patients older than age 16 treated in the MRI era (1986-96). Twelve of the 32 patients demonstrated the well-described desmoplastic pathologic MB variant. Furthermore, the majority (19/32) of tumors were laterally located in the cerebellum. Complete resection was performed in the majority of patients (17/32), subtotal in 6, partial in 5, and biopsy only in 4 patients. All patients received 55 Gy to the posterior fossa and 36 Gy to the entire neuraxis, with 24/32 receiving chemotherapy as well. The 5 and 8 year overall survivals were 83 and 45%, and the disease-free survival rates were 57 and 40%, respectively. Seventeen of the 32 experienced tumor recurrence, with a median follow-up period of 5.4 years, 29% of which occurred more than 5 years after treatment, and with the posterior fossa being the predominant relapse site. In a multivariate analysis, complete resection was predictive of improved posterior fossa control and disease-free survival rates ($P=0.02$). Only 1 of 17 patients who underwent complete resection experienced failure in the posterior fossa, whereas 10 of 15 patients who underwent less than complete resection experienced failure in the posterior fossa. The authors also observed that patients who completed radiotherapy in less than 48 days had fewer recurrences, an observation which likely reflects selection bias. Radiotherapy was delayed in patients receiving chemotherapy, which was given to high-risk patients. This careful analysis is limited by the small number of patients in each subgroup. However, the authors demonstrate that the desmoplastic histologic variant and laterally located tumors are more common in adults. Moreover, in contrast to children, adults tend to experience late relapse more frequently, and therefore, these patients must be followed closely over time. Their finding of the importance of complete resection is in accord with published pediatric data. They rightly point out that the role of chemotherapy in low risk patients is worthy of further investigation.

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Volume: 2, Issue: 2

Title: Long-term visual outcome after non-radical microsurgery in patients with parasellar and cavernous sinus meningiomas

Review Type: Article

Category: Adult Neurosurgery

Journal: Neurosurgery, Vol: 47, No. : pages 24-32, July 2000

Authors: Klink DF, Sampath P, Miller NR, Brem H, Long DM

Summary: This is a much-needed long-term functional follow-up study from the Johns Hopkins group of 29 patients with parasellar or cavernous sinus meningiomas and visual sensory or ocular motor dysfunction at presentation. The strength of this study is that all patients had at least 10 years of follow-up. Nineteen of the 29 patients had unilateral or bilateral optic neuropathy at presentation. The surgical approach was actually quite radical in the extra-cavernous region, corresponding to a Simpson grade I meningioma removal. Tumor progression was experienced in two-thirds of patients during an average follow-up period of 13.6 years, and in 89% of patients during an average follow-up of 15 years. Of the 7 patients who received radiation therapy, two progressed (29%) at 1 and 10 years. Twenty-seven of 29 patients (93%) retained vision of at least 20/40 in at least one eye, and 14 patients (48%) retained vision of 20/40 or better in both eyes. During this follow-up period, new ocular motility deficits developed in only 3 of the 29 patients (~10%), and 7 patients developed a unilateral or bilateral optic neuropathy during a mean follow-up of 13.6 years. They conclude that radical surgery is not required to achieve long-term useful visual function for patients with parasellar or cavernous sinus meningiomas. Moreover, radical surgery may not provide any advantage in improving existing cranial nerve palsies, in delaying or preventing the progression of preexisting cranial neuropathies, or in preventing the development of new cranial neuropathies. In summary, non-radical debulking of extra-cavernous tumor followed by radiation therapy (or perhaps stereotactic radiosurgery) may be the best option for most of these patients, with respect to visual function.

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Volume: 2, Issue: 2

Title: Telomerase activity in primary and secondary glioblastomas multiforme as a novel molecular tumor marker

Review Type: Article

Category: Adult Neurosurgery

Journal: Journal of Neurosurgery, Vol: 93, No. 4: pages 618-625, Oct 2000

Authors: HARADA K, KURISU K, TAHARA H, TAHARA E, IDE T, TAHARA E

Summary: The authors examined telomerase activity, telomerase component expression, and telomere lengths in 42 GBM samples. They classified the tumors as primary (#22) and secondary (#20) glioblastomas, according to the results of assessments of EGFR and MDM2 amplifications, p53 mutation, LOHs in chromosomes 17p and 10, and the patient's clinical course.

They found no significant difference in telomere length between primary and secondary GBMs, but found that secondary GBMs displayed significantly higher levels of telomerase activity and hTERT (human telomerase reverse transcriptase) expression than primary GBMs. Tumors with a p53 gene mutation demonstrated significantly higher telomerase activity than those without a p53 mutation. They hypothesized that telomerase reactivation was a relatively late event in secondary GBMs which occurred after significant telomere shortening and allowed tumor cell proliferation to continue.

Their work explores the distinction between malignant transformation (a multistep process in which mutations of genes activate protooncogenes or negate the action of tumor suppressor genes) and immortalization (the perpetual elongation of telomeric repeats by telomerase that allows cell division to continue). The results further elucidate the distinction between GBMs arising de novo from those evolving from lower grade gliomas and underlines the necessity of a deeper understanding of the genetic characteristics of brain tumors for the purpose of classification and intervention.

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Volume: 2, Issue: 2

Title: Dexamethasone-induced abolition of the inflammatory response in an experimental glioma model: a flow cytometry study

Review Type: Article

Category: Adult Neurosurgery

Journal: Journal Neurosurgery, Vol: 93, No. 4: pages 634-639, Oct 2000

Authors: Badie B, Schartner JM, Paul J, et al.

Summary: The authors examined the effects of dexamethasone on inflammatory cell infiltration in an immunogenic rat glioma model. Using flow cytometry, the extent of microglia, macrophage, lymphocyte, and cytotoxic T-cell infiltration into tumor, tumor periphery, and contralateral tumor-free hemisphere in 11-day-old intracranial C6 tumors that had been excised from dexamethasone-treated and untreated rats was analyzed.

Microglia and Lymphocyte infiltration into tumors was reduced by greater than 50% by a 7-day course of low-dose dexamethasone (0.1 mg/kg/day). A dose of dexamethasone mg/kg/day, further reduced lymphocyte infiltration (89% inhibition) but had no additional inhibitory effect on microglia invasion. Macrophage infiltration of tumors was not inhibited at the dexamethasone doses used in this study.

These results underscore our need for a better understanding of the nature of steroid medication immunosuppression in human gliomas - especially in light of the increasing focus on immunotherapy.

Select Review in Neuro-Oncology

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Volume: 2, Issue: 2

Title: The impact of age and sex on the incidence of glial tumors in New York state from 1976 to 1995

Review Type: Article

Category: Adult Neurosurgery

Journal: Journal of Neurosurgery, Vol: 93, No. 6: pages 932-939, Dec 2000

Authors: McKinley BP, Michalek AM, Fenstermaker RA, Plunkett RJ

Summary: Using data from the New York State Cancer Registry from 1976 to 1995, crude, age-, and sex-specific incidence rates were calculated for three glial tumors: glioblastoma multiforme (GBM), astrocytoma not otherwise specified (ANOS), and anaplastic astrocytoma (AA).

11,204 cases of GBM, 4613 cases of ANOS, and 878 cases of AA were identified with a statistically significant increase in the age-adjusted incidence of GBM and AA during the twenty-year interval. The increase in ANOS incidence was not statistically significant. The incidence of each type of tumor was lower in the female population with the incidence of GBM in males 1.5 to 2 times higher during the ages roughly corresponding to the period of time between menarche and menopause.

This observation suggests a protective effect from female sex hormones. The reason for the increase in incidence cannot be determined from the data available.

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Volume: 2, Issue: 2

Title: Fluorescence-guided resection of glioblastoma multiforme by using 5-aminolevulinic acid-induced porphyrins: a prospective study in 52 consecutive patients

Review Type: Article

Category: Adult Neurosurgery

Journal: Journal of Neurosurgery, Vol: 93, No. 6: pages 1003-1013, Dec 2000

Authors: Stummer W, Novotny A, Stepp H, Goetz C, Bise K, Reulen HJ,

Summary: The authors analyze the influence of fluorescence-guided resection of GBM on postoperative magnetic resonance imaging and survival in a series of fifty-two consecutive patients. 5-aminolevulinic acid (5-ALA), - which is not itself fluorescent but which is metabolized into fluorescent porphyrins in glioblastoma multiforme (GBM) - was administered 3 hours before induction of anesthesia. This agent avoided the difficulties previous studies with blood borne fluorescent agents had experienced with leakage of agent into edematous brain and contamination of the surgical bed by bleeding. Two Intraoperatively fluorescence qualities were described: solid fluorescence felt to represent coalescent tumor and vague fluorescence secondary to infiltrative tumor.

Of 264 biopsy specimens, 211 with macroscopic fluorescence were positive for tumor, however, 26 nonfluorescing specimens contained tumor and 19% of these contained solid tumor. One biopsy specimen showed macroscopic fluorescence but failed to show tumor.

Complete resection of contrast-enhancing tumor was accomplished in 63% of patients and fluorescent tissue left unresected for safety reasons predicted residual enhancement on MR images in 18 of the 19 remaining patients. Age, residual solid fluorescence, and absence of contrast enhancement in MR imaging were independent predictors of survival. There was one case of surgical morbidity but no complications from the agent itself.

This study describes encouraging results with a technique for the intraoperative identification of tumor and raises the question of the true importance of completeness of resection on survival. To address that question and to further explore the efficacy of this technique, the authors have initiated a phase III, multicenter, prospective randomized trial.

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Volume: 2, Issue: 2

Title: Surgical Treatment of Clinically Non-Secreting Pituitary Adenomas in Elderly Patients.

Review Type: Article

Category: Adult Neurosurgery

Journal: NEUROSURGERY, Vol: 47, No. : pages 843-849, 2000

Authors: Kurosaki M, Dukecke DK, Flitsch J and Saeger W.

Summary: This is a retrospective review of their series of 32 patients with non-secreting pituitary macroadenomas over the age of 70 treated with the TNTS approach. They achieved complete resection in 75%, vision improved in 83%, and there was no major surgical or anaesthetic morbidity. For the patient who required re-operation, the median time to recurrence was 13 years. Post-operatively, endocrinologic abnormalities were noted in 84 % of patients with 45% demonstrating reporting new adrenocorticotrophic hormone deficiency. Median post-operative stay was 16.3 days and there was a 16% incidence of CSF leaks.

This study demonstrates that transphenoidal surgery can be safely done in many patients regardless of age provided they meet medical requirements for general anaesthesia. Nonetheless, the length of hospital stay, and relatively high incidence of post-operative endocrinologic abnormalities and CSF leaks suggest that there may be more morbidity in this group of patients, though this issue was not specifically addressed in the paper.

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Volume: 2, Issue: 2

Title: Craniopharyngiomas of the Third Ventricle: Trans-Lamina Terminalis Approach.

Review Type: Article

Category: Adult Neurosurgery

Journal: Neurosurgery, Vol: 47, No. : pages 857-865, 2000

Authors: Maira G, Anile C, Colosimo C, and Cabezas D.

Summary: The authors report their experience with 8 cases of purely intraventricular craniopharyngiomas of the third ventricle approached via the pterional trans-lamina terminalis approach. They achieved gross total resection in 7/8 of the patients with this relatively rare condition with no major operative complications, and no compromise of visual function. No patients were treated with radiotherapy.

It is notable, that 5/8 (63%) of the patients in this series required hormonal replacement therapy post-operatively and 2/8 (25%) died of psychological and endocrinologic complications of treatment 12-27 months post-operatively. The authors emphasize the importance of close endocrine follow-up.

While the authors did not discuss the rationale behind their choice of approach, the commentaries by Drs. Ciric, Patterson and Rhoton offer a good discussion of the various surgical approaches.

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Volume: 2, Issue: 2

Title: Impact of Computed Tomographic and Magnetic Resonance Imaging Findings on Surgical Outcome in Petroclival Meningiomas.

Review Type: Article

Category: Adult Neurosurgery

Journal: Neurosurgery, Vol: 47, No. : pages 1287-1295, 2000

Authors: Carvalho GA, Matthies C , Tatagiba M ,Egnbal R ,and Samii M.

Summary: In this paper, the authors attempt to correlate pre-operative imaging characteristics with extent of resection and outcome in a retrospective review of 70 petroclival meningiomas resected between 1978-1995. They concluded that supra-tentorial tumor extension, peritumoral brainstem edema, and signs of infiltration influenced the extent of resection, while involvement of the inferior cranial nerves and radiological evidence of brainstem edema correlated with long-term functional outcome.

This paper, while thought-provoking, has several limitations. Firstly, it is a retrospective study reflecting primarily the experience of the senior author over a 17 year period, beginning in the pre-MRI era. One would imagine that technological factors such as availability of more advanced technology such as microscopes, CUSA, stereotaxis and imaging influenced the approach and success of the surgeons during this period, as well as the development of new surgical approaches and the experience of the surgeon. Furthermore, while anatomic preservation of cranial nerves was noted, functional preservation was not assessed. Finally, there is no information regarding adjuvant radiotherapy or recurrence rates. Thus, while this study confirms several earlier studies regarding the detrimental effect of brainstem edema and signs of infiltration, their measures of outcome remain somewhat ambiguous. The authors conclusion raises the important question: when should radical surgery be done. The answer awaits future study.

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Volume: 2, Issue: 2

Title: Combined Anterior Craniofacial Resection For Tumors Involving the Cribriform Plate: Early Post-operative Complications and Technical Considerations.

Review Type: Article

Category: Adult Neurosurgery

Journal: Neurosurgery, Vol: 47, No. : pages 1296-1305, 2000

Authors: Solero CS , DiMeco F , Sampath P et al.

Summary: This paper is a retrospective review of 168 consecutive procedures performed 1987-1997 in a single institution. The authors describe a high rate of early complications in their first 30 cases, and the steps they subsequently took to reduce complications in the following 138 patients by nearly half. These include use of a limited craniotomy, reinforcement of the orbital walls, use of a pedicled pericranial flap to repair the floor of the frontal sinus, avoidance of lumbar drainage, and leaving a small hole in the frontal bone for aspiration of tension pneumothorax should one occur.

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Volume: 2, Issue: 2

Title: Is there a benefit of Pre-operative Meningioma Embolization?

Review Type: Article

Category: Adult Neurosurgery

Journal: Neurosurgery, Vol: 47, No. : pages 1306-1312, 2000

Authors: Bendszus M, Rao G, Burger R et al.

Summary: The authors present a prospective study of pre-operative embolization for 60 consecutive intracranial meningiomas at two centers in an effort to evaluate the effect of embolization on blood-loss, difficulty of surgery, and outcome. They found no differences in any of these parameters between the two groups, though they did find that blood loss was less in the subgroup with >90% embolization. Of note, there was also a single neurological deficit attributable to embolization.

There were several flaws in this paper. Although the authors had presented data suggesting that surgical approaches and philosophies were similar in the two centers, this was not a true randomized controlled study, which limits the conclusions which can be drawn. Furthermore, the patients in the groups were quite different, with convexity meningiomas representing 66% of the patients in the surgery only group and 80% of the patients in the embolized group

Select Review in Neuro-Oncology

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

Volume: 2, Issue: 2

Title: Proliferation Index of Non-functioning Pituitary Adenomas: Correlations with Clinical Characteristics and Long-term Follow-up Results.

Review Type: Article

Category: Adult Neurosurgery

Journal: Neurosurgery, Vol: 47, No. : pages 1313-1319, 2000

Authors: Losa M, Franzin A, Mangili F et al.

Summary: The authors present a retrospective study correlating the KI-67 labeling index (LI) in 101 consecutive patients with non-functioning pituitary adenomas with various clinical parameters including tumor recurrence. They hypothesized that if KI-67 LI was predictive of recurrence, it would be useful in determining timing and need for post-op adjuvant radiotherapy.

During a mean follow-up of 40 months, they found a correlation between KI-67 LI and age at surgery, but no correlation with recurrence. In contrast, MRI evidence of cavernous sinus invasion, and previous surgery, correlated positively with recurrence, while age at initial surgery and post-operative radiotherapy correlated inversely with recurrence.

Select Review in Neuro-Oncology

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

Volume: 2, Issue: 2

Title: Growth and migration markers of rat C6 glioma cells identified by serial analysis of gene expression.

Review Type: Article

Category: Basic Science

Journal: *Glia*, Vol: 32, No. 2: pages 146-154, Nov 2000

Authors: Gunnensen JM, Spirkoska V, Smith PE, Danks RA, Tan SS

Summary: SUMMARY:

When a well-characterized and popularly utilized glioma model system is seized for detailed gene expression analysis under controlled conditions, the potential benefit to the research community is large. Gunnensen et al used serial analysis of gene expression (SAGE) to construct the molecular profile of the most abundantly differentially expressed genes in C6 glioma cells referenced against normal rat astrocytes. Many of the genes reported here are familiar players in the emerging field of gene expression profiling of gliomas. These include higher levels of RHAMM, preproenkephalin, osteopontin, and autocrine motility factor; suppressed expression in C6 cells was observed for SPARC, thymosins beta-4 and beta-10, and transgelin. Glioma modelers should be enthused at the concordance demonstrated between this iteration of the C6 and human glioblastomas.

ABSTRACT

Tumors derived from rat C6 cell implants into rat brain exhibit similar morphological characteristics and degree of vascularization to human glioblastomas. To establish a molecular basis for C6 gliosarcoma malignancy, we have constructed a molecular profile of the most abundantly expressed genes, using serial analysis of gene expression (SAGE). Sequence tags (1168) representing 738 individual transcripts were collected and tag-to-gene mapping was carried out using the UniGene data set for rat. Differentially expressed C6 transcripts were identified by comparison of tags collected for C6 cells with a similar number (1002) of tags from a rat primary astrocyte library. Genes found to be expressed at increased levels in C6 cells are associated with cell surface interactions, migration, or metastasis formation and proliferation. These include the receptor for hyaluronan-mediated motility (RHAMM), S-100 related protein 42A, galectin I, preproenkephalin, osteopontin, autocrine motility factor, alpha-tubulin, ad1 antigen, and cofilin. In addition, a tag with no database match probably representing a previously uncharacterized transcript was differentially expressed in C6 cells. Transcripts showing reduced expression in C6 cells relative to astrocytes included the extracellular matrix glycoprotein osteonectin/SPARC (secreted protein, acidic, rich in cysteine), actin-binding proteins thymosins beta-4 and beta-10, the cysteine protease inhibitor cystatin C, the actin-gelling protein SM22/transgelin, and ferritin-H. SAGE results were confirmed by Northern blot for all transcripts tested, reaffirming the value of the SAGE technique for expression profiling in cancer biology.

References: Markert JM, Fuller CM, Gillespie GY, Bubien JK, McLean LA, Hong RL, Lee K, Gullans SR, Mapstone TB, Benos DJ. Differential gene expression profiling in human brain tumors. *Physiol Genomics* 2001 Feb 7;5(1):21-33

Sallinen SL, Sallinen PK, Haapasalo HK, Helin HJ, Helen PT, Schraml P, Kallioniemi OP, Kononen J. Identification of differentially expressed genes in human gliomas by DNA microarray and tissue chip techniques. *Cancer Res* 2000 Dec 1;60(23):6617-22

Select Review in Neuro-Oncology

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

Volume: 2, Issue: 2

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Review Type: Article

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Select Review in Neuro-Oncology

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

Volume: 2, Issue: 2

Title: Astrocyte-specific expression of activated p21-ras results in malignant astrocytoma formation in a transgenic mouse model of human gliomas.

Review Type: Article

Category: Basic Science

Journal: Cancer Research, Vol: 61, No. 9: pages 3826-3836, 2001

Authors: Ding H, Roncari L, Shannon P, Wu X, Lau N, Karaskova J, Gutmann DH, Squire JA, Nagy A, Guha A.

Summary: To date, there are few spontaneously occurring, accurate preclinical models for human astrocytomas. To address this problem, the authors have used an ES cell-based transgenic approach to overexpress oncogenic V12Ha-ras specifically in astrocytes using a GFAP promoter. This gene was chosen because the activation of the p21-ras pathway is functionally important in stimulating astrocytoma proliferation and angiogenesis, and may be a potential therapeutic target with agents that inhibit p21-ras isoprenylation. Two mouse lines were derived. All mice with the highest levels of p21-ras-GTP activity died from malignant astrocytomas within 2 weeks. Those mice with moderate levels died from solitary or multifocal low- and high-grade tumors within 2-6 months. The tumors were morphologically similar to human astrocytomas. In addition, they exhibited molecular alterations associated with astrocytomas including, decreased or absent p16, p19, and PTEN as well as overexpression of EGFR, MDM2 and CDK4. Therefore, this transgenic mouse model recapitulates many of the molecular, histopathologic, and growth characteristics of human astrocytomas in a reproducible, germ-line-transmitted, and high penetrance manner.

Select Review in Neuro-Oncology

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

Volume: 2, Issue: 2

Title: Local endostatin treatment of gliomas administered by microencapsulated producer cells.

Review Type: Article

Category: Basic Science

Journal: Nature Biotechnology, Vol: 19, No. : pages 29-34, Jan. 2001

Authors: Read TA, Sorensen DR, Mahesparan R, Enger PO, Timpl R, Olsen BR, Hjelstuen MH, Haraldseth O, Bjerkvig R.

Summary: Abstract: We describe a technique for the treatment of malignant brain tumors based on local delivery of the anti-angiogenic protein endostatin from genetically engineered cells encapsulated in ultrapure sodium alginate. Alginate consists of L-guluronic and D-mannuronic acid, which in the presence of divalent cations forms an extended gel network, in which cells reside and remain immunoisolated, when implanted into the rat brain. Here, we show that endostatin-transfected cells encapsulated in alginate maintain endostatin secretion for at least four months after intracerebral implantation in rats. During the implantation period 70% of the encapsulated cells remained viable, as opposed to 85% in in vitro-cultured capsules. Rats that received transplants of BT4C glioma cells, together with endostatin-producing capsules (0.2 microg/ml per capsule), survived 84% longer than the controls. The endostatin released from the capsules led to an induction of apoptosis, hypoxia, and large necrotic, vascular areas within 77% of the treated tumors, whereas all the controls were negative. The encapsulation technique may be used for many different cell lines engineered to potentially interfere with the complex microenvironment in which tumor and normal cells reside. The present work may thus provide the basis for new therapeutic approaches toward brain tumors.

COMMENT: In this and in the accompanying report, the authors employ cells, genetically engineered to produce the angiogenic inhibitor endostatin and encapsulated to prevent host rejection, to produce a significant anticancer response in rats with BT4C glioma tumors. The use of encapsulated cells to release angiogenic inhibitor proteins could thus find a role as a local treatment for tumors.

Select Review in Neuro-Oncology

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

Volume: 2, Issue: 2

Title: Continuous release of endostatin from microencapsulated engineered cells for tumor therapy.

Review Type: Article

Category: Basic Science

Journal: Nature Biotechnology, Vol: 19, No. : pages 35-39, January 2001

Authors: Joki T, Machluf M, Atala A, Zhu J, Seyfried NT, Dunn IF, Abe T, Carroll RS, Black PM.

Summary: Research studies suggest that tumor-related angiogenesis contributes to the phenotype of malignant gliomas. We assessed the effect of local delivery of the angiogenesis inhibitor endostatin on human glioma cell line (U-87MG) xenografts. Baby hamster kidney (BHK) cells were stably transfected with a human endostatin (hES) expression vector and were encapsulated in alginate-poly L-lysine (PLL) microcapsules for long-term delivery of hES. The release of biologically active endostatin was confirmed using assays of bovine capillary endothelial (BCE) proliferation and of tube formation. Human endostatin released from the microcapsules brought about a 67.2% inhibition of BCE proliferation. Furthermore, secreted hES was able to inhibit tube formation in KDR/PAE cells (porcine aortic endothelial cells stably transfected with KDR, a tyrosine kinase) treated with conditioned U-87MG medium. A single local injection of encapsulated endostatin-secreting cells in a nude mouse model resulted in a 72.3% reduction in subcutaneous U87 xenografts' weight 21 days post treatment. This inhibition was achieved by only 150.8 ng/ml human endostatin secreted from 2×10^5 encapsulated cells. Encapsulated endostatin-secreting cells are effective for the treatment of human glioblastoma xenografts. Continuous local delivery of endostatin may offer an effective therapeutic approach to the treatment of a variety of tumor types.

COMMENT: In this and in the accompanying paper, cells were genetically engineered to produce endostatin and then encapsulated to inhibit host rejection. The authors show that these cells inhibited the grow of ectopic glioma xenografts in nude mice. These studies provide a promising avenue for the study of this type of delivery for peptide modulators of angiogenesis.

Select Review in Neuro-Oncology

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

Volume: 2, Issue: 2

Title: Inactivation of the DNA-repair gene MGMT and the clinical response of gliomas to alkylating agents.

Review Type: Article

Category: Medical Oncology

Journal: New England Journal of Medicine, Vol: 343, No. 19: pages 1350-4, Nov 9, 2000

Authors: Esteller M, Garcia-Foncillas J, Andion E, Goodman SN, Hidalgo OF, Vanaclocha V, Baylin SB, Herman JG.

Summary: The DNA-repair enzyme O6-methyl guanine-DNA methyltransferase (MGMT) inhibits the action and efficacy of agents such as carmustine (BCNU), procarbazine, and temozolomide by reversing alkylation at the O6 guanine site, thereby stopping the formation of lethal DNA cross links. Conversely, MGMT activity is controlled by a promoter; methylation of this promoter stops production of MGMT and is thought to confer chemosensitivity to treatment with alkylating agents. Chemosensitivity may equate to prolonged survival.

The authors studied frozen tissue specimens from 47 consecutive patients with malignant glioma. The MGMT promoter in tumor DNA was analyzed with a methylation-specific PCR assay and these results were correlated with clinical parameters. Nineteen of 47 patients (40%) demonstrated methylation of the MGMT promoter; methylated and unmethylated samples, although small in total number, were equitably distributed with respect to age, KPS, and histology (astrocytoma WHO grade III [n=18] vs. grade IV [n=29]). Clinically, all patients were treated with intra-arterial cisplatin, 'whole brain' radiotherapy, and a median of three courses of IV BCNU. Twelve of 19 patients with methylated tumors (63%) had a partial (PR) or complete response (CR) to BCNU, as compared to only one of 28 patients with unmethylated tumors (4%) showing radiographic response. The median time to radiographic progression was 21 months in the former group and only 8 months in the latter. The authors conclude that methylation status of the MGMT promoter is an independent and stronger predictor than any other known clinical / pathological parameter used in practice today.

A spirited editorial volley followed the publication of this article. Relevant issues that were raised can be summarized as follows: 1) Multiple treatments were administered in addition to BCNU, therefore response solely to BCNU administration may not a tangible endpoint for this study. 2) It is unclear whether methylation of the MGMT promoter is predictive of the outcome for patients who are not given chemotherapy, particularly BCNU, as part of their primary treatment. 3) In the absence of methylation of the MGMT gene, translational and post-translational processes can alter MGMT levels and functional activity in tumors - this may confound the interpretation of the methylation status of the MGMT gene.

Although a prospective pharmacogenomic study comparing patients who receive monotherapy with IV BCNU to those placed in a placebo group would likely be revealing, this study design poses an ethical dilemma. Perhaps a larger, more homogenous group can be studied in the future (e.g. all patients with glioblastoma), with all patients being followed for survival as an important secondary endpoint. Because state-of-the-art care for patients with glioblastoma multiforme most often calls for multiple, individualized drug regimens, one can concede that the MGMT issue may be very difficult to fully elucidate. Nevertheless, the data presented in this article are compelling and reveal credible evidence of a correlation between survival after BCNU therapy and MGMT methylation.

Select Review in Neuro-Oncology

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

Volume: 2, Issue: 2

Title: Identification of pilocytic astrocytoma and fibrillary astrocytoma as distinct entities.

Review Type: Article

Category: Medical Oncology

Journal: Cancer, Vol: 89, No. 7: pages 1569-76, October 1, 2000

Authors: Fisher PG, Breiter SN, Carson BS, Wharam MD, Williams JA, Weingart JD, Foer DR, Goldthwaite PT, Tihan T, Burger PC.

Summary: The authors performed a single institution retrospective analysis of patients with 'brain stem glioma' in order to elucidate and streamline a clinically relevant and applicable classification scheme. All patients were diagnosed between 1980-1997 and were less than 21 years of age at the time of diagnosis. Clinical parameters investigated include duration of symptoms prior to diagnosis, presence or absence (+/-) of abducens palsy, +/-neurofibromatosis type 1, date of surgery (if performed), placement of shunt for hydrocephalus, initial treatment regimen, date of first relapse, and date of death or last clinical encounter. Radiographic parameters investigated include primary location of tumor, pattern of gadolinium enhancement, +/- dorsal exophytic growth pattern, and +/-basilar artery engulfment.

Seventy-six patients were identified, with initial diagnostic MRI available for 51 and pathology specimens for 48 patients. Twenty cases were classified histologically as pilocytic astrocytoma (PA), 14 as fibrillary astrocytoma (FA), and 14 as other tumors or intermediate astrocytic pathology. For all tumors, characteristics significantly associated with a worse survival rate were: symptom duration < 6 months before diagnosis, abducens palsy at presentation, pontine location, and engulfment of the basilar artery. PA was associated with location outside the ventral pons and dorsal exophytic growth. FA was associated with the poor prognostic factors listed above and had a 1-year overall survival of 23% vs. PA which showed a 5 year overall survival of 95%. Interestingly, grade 2 FA seems to be biologically related to WHO grades 3 and 4.

The authors assert that the disparate 'pathology and location' based classification schemes may be ineffective and that the eligibility criteria for future cooperative trials investigating brain stem glioma should be restructured. Eligibility without biopsy should be restricted to tumors diffusely involving the ventral pons, and these children should be enrolled in progressive, aggressive clinical trials. Most children with focal brain stem glioma are likely to fare well with only limited intervention, commensurate to the clinical scenario.

Select Review in Neuro-Oncology

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

Volume: 2, Issue: 2

Title: Stages of Improvement in Visual Fields After Pituitary Tumor Resection

Review Type: Article

Category: Neuro-Ophthalmology

Journal: American Journal of Ophthalmology, Vol: 130, No. 6: pages 813-820, Dec. 2000

Authors: Kerrison JB, Lynn MJ, et al

Summary: 62 patients were included in this retrospective review of charts of patients with pituitary tumors and abnormal visual fields. They were followed with serial visual fields post-operatively at the following time periods: 1 week, 1-4 months, 6-12 months, 2 years, and 3 or more years. The authors concluded that the pattern of recovery of visual function after decompression of the anterior visual pathways suggests at least three phases of improvement. The early fast phase (surgery to 1 week) of improvement may lead to normalization of visual fields in some individuals. The early slow phase (1 month to 4 months) is the period of most notable improvement. A late phase (6 months to 3 years) of mild improvement does not appear significant overall but may be marked in some individuals. Each of these phases may have one or more biologic mechanisms underlying the observed improvement.

Select Review in Neuro-Oncology

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

Volume: 2, Issue: 2

Title: Expression of p57KIP2 Potently Blocks the Growth of Human Astrocytomas and Induces Cell Senescence

Review Type: Article

Category: Neuro-Pathology

Journal: The American Journal of Pathology, Vol: 157, No. 3: pages 919-932, Sep. 2000

Authors: Atsushi T, Keiichi S, et al

Summary: The authors demonstrate here that inducible expression of p57 in three well-characterized human astrocytoma cell lines (U343 MG-A, U87 MG, and U373 MG) leads to a potent proliferative block in G1. The proliferative block imposed by p57 on human astrocytoma cells results in changes in the expression of a number of cell cycle regulatory factors, cell morphology, and a strong stimulus to cell senescence.

Select Review in Neuro-Oncology

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

Volume: 2, Issue: 2

Title: Astrocytes Give Rise to Oligodendrogliomas and Astrocytomas after Gene Transfer of Polyoma Virus Middle T Antigen in Vivo

Review Type: Article

Category: Neuro-Pathology

Journal: The American Journal of Pathology, Vol: 3, No. 157: pages 1031-1037, Sep. 2000

Authors: Holland EC, Li Y, et al

Summary: The authors report the generation of mixed gliomas from in vivo transformation of glial fibrillary acidic protein (GFAP)-positive cells (differentiated astrocytes) with polyoma virus middle T antigen (MTA). The authors conclude that GFAP- expressing astrocytes, with appropriate signaling abnormalities, can serve as the cell of origin for oligodendrogliomas, astrocytomas, or mixed gliomas.

Select Review in Neuro-Oncology

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

Volume: 2, Issue: 2

Title: Ezrin Immunoreactivity Is Associated with Increasing Malignancy of Astrocytic Tumors but Is Absent in Oligodendrogliomas

Review Type: Article

Category: Neuro-Pathology

Journal: The American Journal of Pathology, Vol: 6, No. 157: pages 1785-1793, Dec. 2000

Authors: Geiger KD, Stoldt P, et al

Summary: The actin-binding protein ezrin has been associated with motility and invasive behavior of malignant cells. The increase of ezrin-IR correlated significantly with increasing malignancy of astrocytic tumors. The results indicate that ezrin-IR may provide a useful tool for the distinction of oligodendrogliomas and astrocytomas and for the grading of astrocytic tumors.

Select Review in Neuro-Oncology

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

Volume: 2, Issue: 2

Title: Radiation-Induced Meningioma: A Distinct Molecular Genetic Pattern?

Review Type: Article

Category: Neuro-Pathology

Journal: Journal of Neuropathology and Experimental Neurology, Vol: 59, No. 7: pages 614-620, Jul. 2000

Authors: Shoshan Y, Chernova O, et al

Summary: The authors observed that unlike sporadic meningiomas, NF2 gene inactivation and chromosome 22q deletions are far less frequent in Radiation-Induced Meningioma, and their role in meningioma development following low dose irradiation is less significant.

Select Review in Neuro-Oncology

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

Volume: 2, Issue: 2

Title: Cytogenetic Analysis of Gemistocytic Cells in Gliomas

Review Type: Article

Category: Neuro-Pathology

Journal: Journal of Neuropathology and Experimental Neurology, Vol: 59 , No. 8: pages 679-686, Aug. 2000

Authors: Kros JM, Waarsenburg N, et al

Summary: In this study gains of chromosome 7 were found in 1 anaplastic astrocytoma, 1 anaplastic oligodendroglioma, and 1 anaplastic oligoastrocytoma. Loss of chromosome 10 was seen in 2 anaplastic astrocytomas, in 1 anaplastic oligodendroglioma, and in 1 anaplastic oligoastrocytoma. In 3 cases, significant differences in spot distributions between gemistocytes and non-gemistocytes were found, but the other cases showed no difference in spot distribution. The authors suggest that although many gemistocytic cells in gliomas may be considered reactive cells, in a subset of tumors, part of the gemistocytic cells should be considered neoplastic.

Select Review in Neuro-Oncology

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

Volume: 2, Issue: 2

Title: Loss of Neurofibromin Is Associated with Activation of RAS/MAPK and PI3-K/AKT Signaling in a Neurofibromatosis 1 Astrocytoma

Review Type: Article

Category: Neuro-Pathology

Journal: Journal of Neuropathology and Experimental Neurology, Vol: 59, No. 9: pages 759-767, Sep. 2000

Authors: Lau N, Feldkamp MM, et al

Summary: Abstract Neurofibromatosis 1 (NF1) is a common autosomal dominant cancer predisposition syndrome, in which 15% to 20% of affected individuals develop astrocytomas. Neurofibromin, the protein product of the NF1 gene, functions as a tumor suppressor. The study supports a role for neurofibromin in the molecular pathogenesis of NF1 astrocytomas.

Select Review in Neuro-Oncology

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

Volume: 2, Issue: 2

Title: Merlin, DAL-1, and Progesterone Receptor Expression in Clinicopathologic Subsets of Meningioma: A Correlative Immunohistochemical Study of 175 Cases

Review Type: Article

Category: Neuro-Pathology

Journal: Journal of Neuropathology and Experimental Neurology, Vol: 59, No. 10: pages 872-879, Oct. 2000

Authors: Perry A, Cai DX, et al

Summary: The molecular pathogenesis of meningiomas is poorly characterized. Loss of NF2 (merlin) expression has been reported in 30%–80% of all sporadic meningiomas. Loss of expression for a second Protein 4.1-family tumor suppressor, DAL-1, is also common. A biologically important role for progesterone receptor (PR) has also been proposed based on its reported inverse relationship with tumor grade. The study concludes that PR immunohistochemistry may have diagnostic utility in meningothelial neoplasms. Protein 4.1-family tumor suppressor losses are likely important early events in meningioma pathogenesis, whereas PR expression is associated with benignity.

Select Review in Neuro-Oncology

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

Volume: 2, Issue: 2

Title: Systemic Metastasis in Glioblastoma May Represent the Emergence of Neoplastic Subclones

Review Type: Article

Category: Neuro-Pathology

Journal: Journal of Neuropathology and Experimental Neurology, Vol: 59, No. 12: pages 1044-1050, Dec. 2000

Authors: Park CC, Hartmann C, et al

Summary: Glioblastomas only rarely metastasize to sites outside the central nervous system. The study summarizes the clinicopathological and molecular genetic findings in 6 patients with metastatic glioblastoma. The observations and a review of the recent literature demonstrate that metastatic glioblastomas tend to occur in younger adults who do not follow long clinical courses, and may be characterized by TP53 mutations and differential clonal selection.

Select Review in Neuro-Oncology

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

Volume: 2, Issue: 2

Title: Cognitive Deficits before Treatment among Patients with Brain Tumors

Review Type: Article

Category: Neuropsychology

Journal: Neurosurgery, Vol: 47, No. 2: pages 324-333, August, 2000

Authors: Tucha, O, Smely, C, Preier, M, & Lange, KW

Summary: Tucha et al can be applauded for their study of patients presenting with intracranial mass lesions prior to receiving any treatment. Their study was designed to examine the frequency of neurocognitive deficits in this population, as well as the patient's perceptions of having such deficits. The authors found a high rate of neurocognitive deficits (91% demonstrated at least one area of deficit; 71% demonstrated at least 3 deficits) but a low rate of patient appreciation of these deficits (only 9% considered themselves neurocognitively impaired). Of note, aside from headache or a single seizure, 59% of their sample demonstrated a normal neurological examination at presentation - indicating that gross deficits in patient behavior, even via professional confrontation, often were not appreciable without neurocognitive testing.

The authors take pains to describe the demographics of their sample, including age, gender, lesion location and lateralization, degree of edema, and percent of patients taking anti-epileptic drugs (AEDs). However, as is often the case, other relevant variables were not captured including education, handedness, level of seizure control, timing of most recent seizure relative to neurocognitive testing, level of pain (headache), role of fatigue (were patients capable of completing this lengthy evaluation in a single setting?), testing in inpatient vs. outpatient setting, neurobehavioral issues such as depression, anxiety, and irritability, and the warranted use of psychoactive medications. As the authors found, simply using lesion location to stratify the sample resulted in insufficient sample size for meaningful comparisons. When dealing with clinical populations, very large samples (the n here = 139) are required to examine relevant variables.

The study design did not include a control group. Inclusion of a suitable control would have increased the confidence in the most pertinent conclusion rendered: that the high rate of deficits was due to brain impairment as opposed to the emotional crisis of experiencing a sudden change in functional status and the new diagnosis of a major medical condition. On the other hand, the authors used standardized neuropsychological tests. Thus, it appears likely their finding of poorer performance in elderly patients, relative to the appropriate norms, will be replicated. One may speculate upon decreased neural reserve due to neuronal drop-out with aging.

The authors note a relative paucity of lateralizing neurocognitive findings, and in particular note that only 1/8 memory tests lateralized. Examination of their choice of tests suggests that tasks of verbal list or verbal paired-associate learning, rather than the Logical Memory and Digit Span subtests, might assess the lateralization hypothesis more comprehensively.

Overall, the author's conclusions on several points are worthy of consideration and follow-up study. For example, patient appreciation of cognitive deficits was notably lower than that indicated by the objective test results; my own clinical practice is consistent with this finding. Another angle on this topic would be to examine whether a loved one's estimate of patient cognitive dysfunction more closely approximates the test results relative to the patient's own estimate. Curiously, the authors did not apply their lateralization data to this finding. By neurological tenet, this application could have suggested anosognosia/anosodiaphoria if the underestimate was more prevalent in those with right-sided lesions. Other reasonable conclusions are that those with greater tumor volumes, and those with the most edema, demonstrated greater (more areas of deficit vs. more severe deficits is not clear) comparative deficits.

This study addresses a complex and worthy issue. Currently, it is difficult to discern what factors account for changes in the neurocognitive status of patients with intracranial mass lesions. Consideration of patient status prior to intervention through surgery, chemotherapy, and radiation therapy is a welcome contribution to this underexplored research area.

Select Review in Neuro-Oncology

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

Volume: 2, Issue: 2

Title: Radiation-Induced Temporal Lobe Changes: CT and MR Imaging Characteristics

Review Type: Article

Category: Neuro-Radiology

Journal: American Journal of Roentgenology, Vol: 175, No. 2: pages 431-436, Aug 2000

Authors: Chong VF-H, Fan Y-F, Mukerji SK

Summary: The film records of 1916 patients with proven nasopharyngeal carcinoma (and all presumably treated with radiation therapy [RT]) were reviewed. After eliminating patients with epidural masses or cavernous sinus involvement (findings which suggest intracranial extension by neoplasm), 47 patients demonstrated intra-axial temporal lobe findings felt to represent radiation change; histologic confirmation was available in only one patient. Average follow-up time interval from completion of RT was 2.6 years.

The CT imaging characteristics of presumed radiation change included ill-defined contrast enhancement (79%), foci of solid enhancement (18%) and an area of ring enhancement (3%). MR imaging characteristics of presumed radiation change included simultaneous gray matter and white matter involvement (65%) and gray matter involvement only (35%).

Comments:

With respect to nasopharyngeal carcinoma previously treated with RT, as intracranial spread by recurrent/residual neoplasm is almost always extra-axial, intra-axial abnormalities involving the inferomedial temporal lobes can be assumed to represent radiation change and not spread of neoplasm.

However, while the intra-axial findings described in this series almost certainly do represent radiation change, they remain non-specific and could still have represented residual/recurrent tumor particularly if a primary (intra-axial) glioma had been the initially treated neoplasm. As is usually the case, when imaging is performed between 3-6 months and 2-3 years after completion of RT, newly developing areas of abnormal enhancement in the brain with or without associated mass effect, in or near the site of a previously treated neoplasm, could represent recurrent/residual neoplasm or radiation change. While PET scanning can be useful in such patients, such scanning is not widely available and biopsy will often still be necessary.

Select Review in Neuro-Oncology

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

Volume: 2, Issue: 2

Title: Malignant Gliomas: MR Imaging Spectrum of Radiation Therapy and Chemotherapy-induced Necrosis of the Brain after Treatment

Review Type: Article

Category: Neuro-Radiology

Journal: Radiology, Vol: 217, No. 2: pages 377-384, Nov 2000

Authors: Kumar AJ, Leeds NE, Fuller GN et al

Summary: The authors reviewed 148 patients who underwent resection of malignant (high grade) gliomas who were then treated with radiation therapy (RT) and chemotherapy and imaged with MR on a regular basis (6-8 week intervals for the first year, every 3-6 months in subsequent years).

Follow-up biopsy of lesions suspicious for recurrent neoplasm was performed in 36 patients (32 patients between 3 and 24 months after completion of RT, and 4 patients between 2 and 3 years after completion of RT). Histologically, 20 patients demonstrated pure radiation necrosis (RN) and 16 demonstrated predominantly RN though limited residual/recurrent tumor was also present.

The MR imaging features of lesions due to RN (or lesions that are primarily due to RN) are described with the following conclusions drawn:

- a) if a tumor was initially non-enhancing and the patient develops an enhancing lesion after RT, RN should be considered
- b) if an enhancing lesion distant from the primary tumor site develops, consider RN
- c) multiple enhancing lesions could represent RN and do not necessarily imply recurrent multicentric glioma
- d) a periventricular location of a new lesion should suggest RN
- e) a soap bubble or Swiss cheese appearance to a new enhancing lesion should suggest RN

The authors stress the importance of considering radiation necrosis in these patients and not necessarily assume that a new enhancing lesion represents recurrent tumor.

Comment: While this article contains nice descriptions of the MRI appearance of pathologically proven radiation necrosis, no attempt was made to compare those findings to the imaging features of patients with proven recurrent tumor (occurring in a similar time-frame to those patients reported in this study). Therefore, the specificity/sensitivity of the MRI features of RN for each of the above-described imaging findings remains unknown. As such, as is well-known, when one has a patient with new MR lesions (new areas of enhancement, new mass effect, etc) arising between 3 months and 3 years after completion of radiation therapy, it remains difficult to delineate between radiation necrosis and recurrent tumor and biopsy will often still be necessary.

Select Review in Neuro-Oncology

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

Volume: 2, Issue: 2

Title: Prognostic factors in intracranial ependymomas in children

Review Type: Article

Category: Pediatrics/Pediatric Neuro-Oncology

Journal: Journal of Neurosurgery, Vol: 93, No. 4: pages 605-613, October, 2000

Authors: DOMINIQUE FIGARELLA-BRANGER, M.D., PH.D., MURIEL CIVATTE, M.D

Summary: This is a retrospective study of 37 children treated at one institution for intracranial ependymomas. The prognostic relevance of patient age and sex, extent of tumor removal, location of the tumor (supratentorial vs. infratentorial, median vs. lateral), tumor histology, and adjuvant therapies in affecting the 5-year progression-free survival (PFS) rate and overall survival (OS) rate were analyzed by univariate and multivariate statistical analyses.

The 5-year OS and PFS rates were 45% and 25%, respectively (median follow up 34 months). By univariate analysis, the authors found that total surgical resection (as confirmed by post-operative MRI) and a median infratentorial location were associated with better outcome. Histological features of anaplasia (specifically endothelial proliferation, necrosis, and more than five mitotic figures per 10 hpf) and younger patient age were negative predictors of outcome. Ki-67 labeling index (LI) negatively correlated with prognosis but the authors note that the Ki-67 LI is highly influenced by technique and is only indicative of a putative biological behavior and as such cannot be used as a definitive prognostic marker. They found that neither adjuvant radiotherapy nor chemotherapy affected prognosis.

This is a thorough and well-written article that is hampered somewhat by small numbers of individuals within subsets. The implication of this paper is that there is a subset of patients who have had gross total resection who should not be given adjuvant therapy.

Determination of the most appropriate and relevant classification of ependymomas is needed and prospective randomized studies to evaluate the efficacy of different forms of classification and treatment will have to be performed.

Select Review in Neuro-Oncology

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

Volume: 2, Issue: 2

Title: Intratumoral therapy with bleomycin for cystic craniopharyngiomas in children.

Review Type: Article

Category: Pediatrics/Pediatric Neuro-Oncology

Journal: Pediatric Neurosurgery, Vol: 33, No. 4: pages 211-218, Oct. 2000

Authors: Hader, WJ, Steinbok, P, Hukin, J, and Fryer C.

Summary: Surgical extirpation of craniopharyngiomas is associated with a significant rate of neurological, visual and endocrinological morbidity and with recurrence. Systemic chemotherapy has proven relatively ineffective, while radiotherapy and radiosurgery pose long-term risks of both morbidity and secondary malignancy, particularly in children. In predominantly cystic lesions, minimally invasive alternatives, including catheter cyst drainage and intra-tumoral chemotherapy, are available.

Hader and colleagues performed a retrospective review of 9 consecutive pediatric patients with a primary diagnosis of cystic craniopharyngioma (n=7) or recurrence (n=2). All were treated at a single, tertiary care center (British Columbia Children's Hospital), between 1994 and 2000. Clinical follow-up averaged three years, and mean age was 7 years.

All nine patients underwent stereotactic or direct placement of intra-tumoral cyst catheters. Two patients did not receive bleomycin: one with extra-cystic leakage on post-operative injection of the cyst catheter with contrast material, and one with multiple, separate cysts. Seven patients received intra-cystic bleomycin. 5 patients experienced a decrease in tumor size subsequent to bleomycin therapy and two progressed. Three patients underwent subsequent microsurgery: two for progression and one for headaches despite a 50% reduction in tumor/cyst size after bleomycin. One patient suffered from peritumoral edema related to bleomycin injection, resulting in worsened endocrine function.

Bleomycin presents a relatively safe, minimally invasive adjunct for the management of cystic craniopharyngiomas in children. In this study, open cyst catheter placement and transventricular cyst catheter placement were anecdotally associated with leakage and/or operative complications. Stereotactic, transparenchymal cyst catheter placement may be preferable.

Select Review in Neuro-Oncology

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

Volume: 2, Issue: 2

Title: Optic pathway gliomas in children under three years of age: The role of chemotherapy

Review Type: Article

Category: Pediatrics/Pediatric Neuro-Oncology

Journal: Pediatric Neurosurgery, Vol: 33, No. 3: pages 151-158, Sept. 2000

Authors: Madeira Silva, M, Goldman, S, Keating, G, Marymount, MA, Kalapurakal, J and Tomita, T.

Summary: Optic pathway/hypothalamic gliomas (OHPGs) occur most commonly in childhood, and often before the age of three. Treatment options in this age group are limited by the developmental and endocrine morbidity of radiotherapy and the visual, neurological and endocrine morbidity of surgery. In recent years, well-tolerated and effective chemotherapeutic regimens have been developed for the treatment of this disease: most prominently combined therapy with carboplatin and vincristine.

Tomita and colleagues report their retrospective review of 20 consecutive patients younger than 3 years of age at diagnosis managed at a single tertiary center (Children's Memorial Hospital, Chicago) over a ten year period ending in 1998. Clinical follow-up ranged from 1.25 to 11 years. 6 patients who underwent observation or surgery alone were excluded.

Of the 14 study patients subjected to chemotherapy, most presented with hydrocephalus and/or ocular symptoms. 6 had diencephalic syndrome. 3 met clinical and radiographic criteria for neurofibromatosis. Five patients underwent partial tumor resection and 4 underwent endoscopic biopsy. Pathology in these cases was universally juvenile pilocytic astrocytoma or low grade glioma. Chemotherapy consisted of carboplatin (n=8), carboplatin/vincristine (n=4) or other agents (n=2). 57% of patients had a sustained reduction in tumor size (1.25 to 8 years). The 5 year progression free survival rate was 63%. In this study, patients who underwent partial surgical resection prior to chemotherapy had a relatively high incidence of tumor progression during or after chemotherapy.

These authors conclude that chemotherapy is a safe and effective option for the early management of OHPGs in young children, serving to control disease and defer, perhaps indefinitely, the use of radiotherapy. Partial surgical resection did not appear to offer significant benefit in this small series.

Select Review in Neuro-Oncology

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

Volume: 2, Issue: 2

Title: Combined postoperative irradiation and chemotherapy for anaplastic ependymomas in childhood: Results of the German prospective trials HIT 88/89 and HIT 91.

Review Type: Article

Category: Radiation Oncology

Journal: International Journal of Radiation Oncology Biology Physics, Vol: 46, No. 2: pages 287-295, 2000

Authors: Timmerman B, Kortmann R-D, Kuhr J, et al.

Summary: Ependymomas account for 3-4% of childhood cancers. This article reports on the results of two German trials conducted by the German Pediatric Hematology and Oncology Group which enrolled 55 patients with anaplastic ependymomas between 1989 and 1997. The goal of the trials was to test adjuvant chemotherapy before XRT and to determine prognostic variables. There was central pathology and radiology review as well as standard follow up imaging every six months. The extent of surgical resection was determined by postoperative CT/MRI. Median follow up was 38 months.

The HIT 88/89 trial was a pilot trial of preirradiation chemo consisting of ifosfamide, VP-16, cisplatin, and cytarabine which had a 55% CR and PR rate. HIT 91 randomized patients between the HIT 88/89 arm and concurrent vincristine with XRT followed by maintenance chemotherapy for 8 cycles. The XRT was delivered in a similar fashion in all arms. Infratentorial and spinal metastatic tumors were treated with 35.2 Gy to neuroaxis (craniospinal XRT) followed by a total dose to gross disease of at least 50 Gy. Supratentorial tumors were treated with a limited volume to 54 Gy.

There was no difference between the randomized arms in HIT 91. 3 year overall survival was 75% and progression-free survival was 60%. Age, sex, and tumor site had no effect on outcome. Stage was crucial as all children with positive cytology or spinal metastases at diagnosis died within two years. This certainly makes one question the benefit of chemotherapy. The extent of surgery was critical. Those with a macroscopically complete resection had a 3 year survival of 92% versus 56% for those with residual disease. The survival for patients with infratentorial tumors treated with CSI XRT was the same as patients with supratentorial tumors treated only locally. As most of the failures were local, the omission of CSI for the supratentorial group was felt by the authors to be justified. In the infratentorial group, the spinal relapse rate was quite low and the need for CSI needs to be further studied. Despite XRT, 80% of failures were local and only 20% were distant. No dose response was discerned due to the uniform radiation guidelines.

My impression is that dose escalation using stereotactic fractionated techniques would be the next logical step for those with gross residual disease despite optimal surgery. The current XRT dose is inadequate. The role and timing of chemotherapy is unknown despite a good reported response rate. The necessity of craniospinal XRT for infratentorial tumors deserves further study. The importance of pathologic review cannot be overstated. 16 of 71 patients treated on the protocol were excluded due to incorrect diagnoses at pathologic review. Most were ependyoblastoma or medulloblastoma. Overall, this study is a valuable addition to the literature on this rare entity.

References: Sunjneen Shah, M.D.

Select Review in Neuro-Oncology

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

Volume: 2, Issue: 2

Title: Conventionally Fractionated Stereotactic Radiotherapy for Acoustic Neuromas

Review Type: Article

Category: Radiation Oncology

Journal: Int J Radiat Oncol Biol Phys, Vol: 48, No. 5: pages 1381-87, Dec, 2000

Authors: Fuss M; Debus J; Lohr F; Huber P; Rhein B; Engenhardt-Cabillic R, Wannemacher M.

Summary: The authors from the University of Heidelberg in Germany report on a series of 51 patients with acoustic neuromas treated with fractionated stereotactic radiotherapy. The patients were treated from 11/89-9/99. Only 42 of the patients had follow-up of greater than a year and are thus the group reviewed in the article. Mean follow-up was 42 months (range 17-131 months).

The patients were treated to a mean prescribed dose, to the 90% line, of 57.6 +/-2.5 Gy with fractions of 1.8 to 2 Gy daily. The target encompassed in the 90% line was the contrast enhancing tumor plus a margin of 2mm. The mean tumor volume was 8.6 cm³ with a median volume of 5.5 cm³. Actuarial tumor control at two years was 100% and 95% at five years with only one patient failing at 26 months. 27 of the patients with follow-up of greater than 12 months had useful hearing prior to therapy. 85.2% of those patients were able to preserve useful hearing at both 2 and 5 years after treatment. In the non NF2 patients hearing preservation was 100% at both 2 and 5 years, compared to 56% (also at both 2 and 5 years) in the NF2 patients (p=.0002). Normal facial nerve function was preserved in all patients whom had not had problems prior to treatment. There were two new cases of trigeminal nerve dysesthesia reported without the denominator noted (presumably 2/42=4.8%).

The authors conclude : "Fractionated stereotactic radiotherapy for acoustic neuromas has been shown to be an effective means of short- and long-term tumor control. Excellent neurofunctional outcome in terms of hearing preservation and function following FSRT has been achieved. Treatment results were equally excellent for both small and large tumors. FSRT may be treatment of choice for patients with only one hearing ear and patients with the associated diagnosis of NF2."

Certainly, radiobiologic principles would predict less neurologic dysfunction with fractionated treatment versus single fraction radiosurgery. The authors, albeit with fairly small numbers and relatively short follow-up, present data with excellent tumor control rates as well as excellent hearing preservation rates. This series of patients, as well as others previously reported, will with longer follow-up help further define the role for fractionated stereotactic radiosurgery in the treatment of acoustic neuromas, with one of the obvious goals being preservation of neurologic function while maintaining tumor control.

Select Review in Neuro-Oncology

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

Volume: 2, Issue: 2

Title: Prognostic Significance of the Time of Developing Motor Deficits Before Radiation Therapy in Metastatic Spinal Cord Compression: One-Year Results of a Prospective Trial.

Review Type: Article

Category: Radiation Oncology

Journal: Int J Radiat Oncol Biol Phys, Vol: 48, No. 5: pages 1403-8 , Dec. 2000

Authors: Rades D; Blach M; Bremer M; Wildfang I; Karstens J; and Heidenreich F.

Summary: The authors from the Hannover Medical University in Hannover, Germany publish the results of their prospective trial of patients with motor deficits at the time of presentation with spinal cord compression from metastatic disease. There was no randomization of the trial as the only factors under review were patient factors.

All of the patients were treated with standard palliative radiation regimens (30Gy/10 37.5Gy/15 or 40Gy/20) with the fields including either one or two vertebral bodies above and below the site of compression.

The authors found that in patients that had motor deficits for more than 14 days prior to initiation of radiation treatment that 93% had improvement in motor function with 82% maintaining ambulatory status 24 weeks post XRT. This is compared with only 10% of patients with improvement in motor function in those with symptoms for 1-14 days. Also, in the 1-14 day group only 41% remained ambulatory. The results were even more dismal for motor symptoms of less than 48 hours duration with 0% with improvement and 25% ambulatory at six weeks.

The findings are rather intriguing and suggest that different pathophysiology may be involved in acute deterioration versus more slowly developing deficits. It has been hypothesized that acute deterioration may be a result of the disruption of the arterial circulation followed by cord infarction and that the more slowly developing process is a result of venous congestion. Presuming that to be true, a powerful argument could be made for the strong consideration of surgical intervention followed by post-operative radiation treatment in those patients with rapidly developing motor weakness as a result of cord compression from metastatic disease. This would allow for a much more rapid recovery of circulation and hopefully better neurologic function.

Select Review in Neuro-Oncology

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

Volume: 2, Issue: 2

Title: Preliminary report of RTOG 9508: A phase III trial comparing whole brain irradiation alone versus whole brain irradiation plus stereotactic radiosurgery for patients with two or three unresected brain metastases

Review Type: Meeting Abstract

Category: Radiation Oncology

Journal: Proceedings of ASTRO (International Journal of Radiation Oncology Biology Physics), Vol: 48, No. 3 (supplement): pages 113-114, October, 2000

Authors: Sperduto PW, Scott C, Andrews D, et al

Meeting: American Society for Therapeutic Radiology and Oncology 42nd annual meeting (Boston), October 22-26, 2000

Summary: This is a preliminary report of a phase III trial conducted by the RTOG (Radiation Therapy Oncology Group) to evaluate the role of stereotactic boost following whole brain radiation (WBRT) for patients with 1-3 metastatic lesions. In 1999 the University of Pittsburgh published the results of their single institution phase III experience with a similar study (WBRT +/- SRS boost for patients with 2-4 metastases). That study closed early (n=27) because of a statistically dramatic difference in outcome favoring the SRS (Gamma Knife)-boosted group (local control = 0% in the WBRT- alone arm versus 92% in the SRS-boosted arm). This report led many to conclude that a boost following WBRT should be the standard of care in similar patient populations, and the results of the phase III RTOG trial were eagerly awaited.

Eligibility for RTOG 9508 included patients with 1-3 brain metastases from a solid malignancy, Karnofsky performance status ≥ 70 and tumor diameters < 4 cm. Patients with single unresectable metastatic lesions were entered on the study, but were not included in the abstract since that arm of the study remains open. 144 patients were randomized to whole brain radiation (37.5 Gy in 15 fractions) plus or minus SRS boost. Median survival for the two groups was 5.3 and 6.7 months respectively (not statistically significant). Brain metastases was reported as the cause of death in 33% and 35% of each group respectively (not statistically significant). Failure rate within the "target volume" (presumably this means within the sites of original intracranial disease) was lower in the SRS- boosted group, 21% versus 37% but this was not statistically different.

At the meeting it was reported that there was a statistically significant benefit in the quality of life analysis with respect to steroid dependency 9 months after treatment favoring the SRS boosted group (73% vs 33%), however, many of the other quality of life measurements were not yet available.

The interpretation of this trial engendered much debate at the ASTRO meeting in terms of what can now be considered "standard of care". Why is the outcome of the RTOG trial so different from the Pittsburgh trial? Are the two patient populations, one from a single institution and the other multi-institutional, somehow fundamentally different? Is there a difference between treatment units, technique, or experience? Is it possible that there is a subset of the RTOG 9508 population for whom there is a local control benefit (perhaps defined by histology or other factors not yet reported)? The argument to utilize SRS boost to decrease steroid dependency for those patients still alive 9 months after WBRT is a compelling one given the good therapeutic index and toxicity profile of SRS for metastases. However, the final verdict with respect to SRS boost for brain metastases at the time of diagnosis will not be in until the full results of the trial become available.

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Select Review in Neuro-Oncology

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

What's Hot in Neuro-Oncology

Volume: 2, Issue: 2

Title: Proxima Therapeutics' Gliasite Radiation Therapy System: Newly FDA Approved for Malignant Brain Tumors

Category: Adult Neurosurgery

Contributor(s): Stephen B. Tatter, M.D., Ph.D.

Institution: Wake Forest University Baptist Medical Center, Winston-Salem, NC

Summary: The Gliasite RTS¹ is one of only three new treatments approved for malignant gliomas in the last 20 years. It consists of an inflatable balloon catheter that is placed in the resection cavity at the time of an otherwise-indicated tumor debulking. Internal radiation is delivered with an aqueous solution of organically-bound ¹²⁵I (Iotrex). [Stubbs, 2000] A 2, 3, or 4 cm diameter Gliasite RTS catheter is implanted. 1-2 weeks later, the device is filled with Iotrex and saline for 3-6 days, whereupon the Iotrex is retrieved. Prescription doses from 40-60 Gy at 0.5-1 cm from the balloon surface have been used in small series of patients with previously-radiated, recurrent, malignant gliomas without the need for reoperation for radiation necrosis.² Initial clinical use demonstrates excellent conformance of brain to the semi-rigid spherical balloon placed in the resection cavity allowing a high radiation dose to be delivered to the volume at greatest risk of recurrence.²

The arguments for delivering additional local radiation to malignant gliomas without necessitating a high rate of reoperation for radiation necrosis are compelling but not yet overwhelming. They include:

- Radiation is by far the most effective treatment for malignant gliomas but presumably due to increasing normal tissue injury there is no net benefit achieved by delivering additional fractionated, external-beam, radiation dose.
- Global control cannot be achieved without achieving local control. 80-90% of recurrences are within 2 cm of the resection cavity margin. [Lee, 1999; Sneed, 1994; Wallner, 1989]
- There is a dose response for seed based brachytherapy in the local control of malignant gliomas. [Sneed, 1996] Due to the inhomogeneity of radiation dose delivered by seed based techniques reported rates of reoperation for radiation necrosis are 26-64%. [Ling, 1979; Saw, 1989; Prados, 1992; Scharfen, 1992; Bernstein, 1994; Wen, 1994] This suggests that there is little room for further refinement of the older technology. It may also explain why seed based brachytherapy has frequently but not uniformly been found to be beneficial. [Laperriere, 1998; Videtic, 1999; Halligan, 1996; Gaspar, 1999; Prados, 1992; Scharfen 1992; Wen, 1994]
- The last more subtle argument is that the rarely observed long-term survival of patients with malignant gliomas is likely at least in part achieved by activating host (presumably immune) defenses. Most of these patients have had multiple recurrences and have undergone multimodal therapy before achieving long-term remission. Among current long-term survivors many have had seed based brachytherapy. Some have had bacterial infections that may have lead to more efficient immune activation. Local tumor killing with radiation has the benefit of allowing tumor antigens to be presented to the immune system which might sometimes result in recognition of the glioma cells as malignant.

The Gliasite RTS offers the potential to improve quality of life during treatment by avoiding the need for external hardware. While FDA approval is based on device performance and safety data and the historically documented benefit of brachytherapy, the Gliasite RTS also offers potential efficacy advantages. Chief among these is the potential for quantitatively studying and optimizing dose. This possibility is unique to the Gliasite RTS among brachytherapy modalities because the catheter functions as a single point source of radiation eliminating spacial distribution of radiation sources as a dependent variable that cannot be studied and optimized. [Dempsey, 1998; Monroe, 2001]

Although tested against recurrent malignant gliomas (anaplastic astrocytoma, anaplastic oligodendroglioma, anaplastic mixed oligoastrocytoma, and glioblastoma multiforme) the Gliasite RTS has been approved by the US FDA for use against "malignant brain tumors." Trials are underway for isolated brain metastases and for newly diagnosed glioblastoma. The case for use of the Gliasite RTS for metastases in order to avoid or delay whole brain radiation is particularly compelling for those of us who have seen patients die of radiation induced dementia in the setting of tumor remission.

In summary, the Gliasite RTS performs safely and efficiently in initial clinical use. Brain conformance to the device after the resection of recurrent malignant gliomas is excellent allowing delivery of a readily-quantifiable radiation dose to the tissue at highest risk for recurrence. This device preserves quality-of-life better than older brachytherapy techniques.

Applications are anticipated in a variety of newly-diagnosed, metastatic, and recurrent brain tumors.

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Phone: 1-770-753-4848
WWW: <http://www.proximatherapeutics.com>
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