



SELECT REVIEW IN NEURO-ONCOLOGY



Editor-in-Chief
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Charlotte, North Carolina



Volume 2, Issue 1
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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.

If you would like to be notified when new issues of Select Review in Neuro-Oncology are released, join the notification listserv. This is a private listserv that will be limited to letting you know when the next issue of Select Review has been released. Go to <http://www.neurosurgery.org/listserv/subunsub.html> to register.

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Adult Neurosurgery

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Select Review in Neuro-Oncology

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Volume: 2, Issue: 1

Title: Brain Tumor Surgery with the Toronto Open Magnetic Resonance Imaging System: Preliminary Results for 36 Patients and Analysis of Advantages, Disadvantages and Future Prospects

Review Type: Article

Category: Adult Neurosurgery

Journal: Neurosurgery, Vol: 46, No. 4: pages 860-867, April 2000

Authors: Bernstein M

Summary: The authors describe their preliminary experience with intraoperative MRI. As expected, the ability to evaluate the surgical approach and the extent of resection and to rule out postoperative complications in real time during the operation was advantageous.

Problems included restricted access to the patient and inconsistent image quality.

No clinical outcome studies have been performed to evaluate the overall benefit of this method to more traditional surgical methods.

Select Review in Neuro-Oncology

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Volume: 2, Issue: 1

Title: Using Proton Magnetic Resonance Spectroscopic Imaging to Predict in Vivo the Response of Recurrent Malignant Gliomas to Tamoxifen Chemotherapy

Review Type: Article

Category: Adult Neurosurgery

Journal: Neurosurgery, Vol: 46, No. 2: pages 306-318, February, 2000

Authors: Preul M, Caramanos Z, Villemure J-G, Shenouda G, LeBlanc R, Langleben A, and Arnold D.

Summary: Because malignant gliomas are rapidly progressive and are highly variable in their response to chemotherapeutic agents, it would be advantageous to identify characteristics predictive of response to various agents prior to instituting therapy, or early in the course of treatment. The authors retrospectively attempted to identify image characteristics which differentiated responders from non-responders to tamoxifen in a group of 16 patients with recurrent malignant glioma using proton magnetic resonance spectroscopy (1H-MRSI). They demonstrated that while there was no difference in choline metabolites between the two groups of patients, lactic acid, and lipid signals were lower in the responders prior to treatment and decreased with time. In contrast, creatine and N-acetyl groups were higher at the outset in responders and stayed relatively constant in both groups. These results present the intriguing possibility of using non-invasive methods to objectively select treatment modalities and assess results prior to clinical or radiographic recurrence. This is clearly a desirable goal. Nonetheless, it is not well understood what these signal changes represent, or whether they correlate specifically to tamoxifen response or may be applicable to other agents. One interpretation might be simply that tumors with the least necrosis (and hence lower lactic acid and lipid signals) had the best prognosis and response to treatment. This approach merits further investigation.

Select Review in Neuro-Oncology

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Volume: 2, Issue: 1

Title: Gamma surgery for vestibular schwannoma

Review Type: Article

Category: Adult Neurosurgery

Journal: Journal of Neurosurgery, Vol: 92, No. : pages 745-759, May 2000

Authors: Prasad D, Steiner M, Steiner L

Summary: Prasad et al present an important addition to the ongoing and raging debate on the appropriate modern treatment for acoustic neuroma. They present their results from 200 cases treated over the past 10 years with Gamma Knife radiosurgery at the University of Virginia. The series appears to be neither consecutive nor inclusive of all patients treated on that unit, although this cannot specifically be concluded from the demographics presented.

The paper opens with a strong section which is a comprehensive and at times touching anecdotal history of the development of the Gamma Knife for radiosurgical treatment of acoustic neuromas. Dr. Steiner was there from the start, and his personal insights are valuable and even humorous.

The series of patients then suffers from the usual ills befalling most radiosurgical and, to be fair, surgical series. Methods including dosing and planning varied over the 10-year study period. Follow-up data range from as little as 1 year up to 10 years. Only 95 patients of the 200 reported had follow-up more than 5 years. In fact, the mean series follow-up is only 4.27 years, testifying to a preponderance of patients with short follow-up. No data are given on the characteristics of the group lost to follow-up so meaningful comparisons with the patients with follow-up are hard to form. Moreover, only 153 of the 200 patients had any kind of follow-up data at all.

In examining the group with the longest follow-up, it appears that 6% of patients will have tumors that enlarge, failing radiosurgery. Another 17% will have tumors that do not change in size, begging the question of efficacy of the treatment. Useful data are presented on the evolution of imaging changes with time. Only 3 patients had facial nerve dysfunction, one of which resolved completely. Only 1.7% of patients without prior symptoms had new and permanent V nerve dysfunction. Fifty-eight per cent of patients with useful hearing pre-operatively retained useful hearing after Gamma Knife. Most importantly, hearing changes began in the majority after 2 years and continued into the 8th post-treatment year. This is at odds with data from the University of Pittsburgh showing a leveling off of hearing changes after the first three years. Explanations are not given for this discrepancy. Patients with smaller tumors had higher hearing preservation rates, similar to the microsurgical experience. Thirteen Gy was the dose at which a statistically higher rate of hearing preservation was found. This matches reports from other institutions.

The discussion in this paper spends far too much time touting the software developed at the author's institution for measuring tumor volumes. Virtually all practitioners in this day and age are familiar with volumetric imaging. The strongest part of this paper is the extensive comparison of radiosurgery to microsurgery for acoustic neuromas. While most of this has been covered before, Prasad et al. summarize the discussion and organize the debate admirably. In doing so, they create an invaluable resource for someone new to the dialogue. It is becoming quite clear that bad Gamma Knife is probably better than bad microsurgery for acoustic neuromas. That is to say, if someone has little experience with this tumor, then Gamma Knife treatment is likely to yield better results than an ill-advised surgical foray. Still, Prasad et al. present one of the more balanced views of the facial nerve and cochlear nerve preservation rates with Gamma Knife, rightfully taking into account the facial paresis encountered by those patients who fail radiosurgery and have subsequent microsurgery. Given the extensive review, then, it is disappointing that short shrift is given to the two major unknowns in radiosurgery: long-term control rates and long-term complications. A passing mention is made of the fact that the lower doses used more recently in radiosurgery may result in poorer long-term control. This is a critical issue. Lastly, what level of long-term complications will we be willing to endure? Will a 1% incidence of radiation-induced malignancy at 30 years be acceptable in the treatment of a benign disease with a proven surgical cure? These are questions that will be answered by further thoughtful and honest reviews of radiosurgical data such as the one presented here.

Select Review in Neuro-Oncology

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

Volume: 2, Issue: 1

Title: Long survival and therapeutic responses in patients with histologically disparate high-grade gliomas demonstrating chromosome 1p loss

Review Type: Article

Category: Adult Neurosurgery

Journal: Journal of Neurosurgery, Vol: 92, No. : pages 983-990, June 2000

Authors: Ino Y, Zlatescu MC, Sasaki H, Macdonald DR, Stemmer-Rachmaninov AO, Jhung S, Ramsay DA, von Deimling A, Louis DN, Cairncross JG

Summary: This is a provocative paper by the Cairncross group that attempts to extend the interest in chromosome 1p deletions found in oligodendrogliomas to the group of tumors that are purely astrocytic, specifically glioblastomas. Cairncross has earlier shown that loss of heterozygosity at chromosome 1p is a powerful predictor prolonged survival and response to PCV chemotherapy in patients with brain tumors possessing oligodendroglioma features on histopathologic diagnosis (1). This is the first useful molecular biological test with clinical utility in brain tumor patients and as such is hopefully a harbinger of molecular classification of brain tumors with clinical prognostic power.

In this small paper, Cairncross and associates, including David Louis and Andreas von Deimling, sought out 7 unusual cases of high-grade astrocytic tumors with unusually long survivals or good responses to chemotherapy. As it turned out, all 7 tumors, retrospectively examined, featured LOH of chromosome 1p. For the sake of comparison, they looked at anonymous samples of some 52 other high-grade astrocytic tumors and only found 1p deletions in 10% of the population. Of course, it's obvious why this paper was published in JNS and not a more, shall we say, widely read cancer journal. This is a molecular biological hors d'oeuvre and not the hearty prospective series of high-grade gliomas that we expect will follow shortly. Nonetheless, this paper shows that we can expect to find 1p deletion in up to 10% of high-grade astrocytic tumors. Moreover, the paper hints that this 10% of an otherwise doomed population may in fact have a longer clinical survival and improved outcome. Moreover, this paper supports the notion that all involved in neuro-oncology must support more widespread use of molecular pathological diagnosis or else be left behind.

References: Cairncross JG, Ueki K, Zlatescu MC, et al: Specific genetic predictors of chemotherapeutic response and survival in patients with anaplastic oligodendrogliomas

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Volume: 2, Issue: 1

Title: Clinical Evaluation And Follow-up Results For Intraoperative Magnetic Resonance Imaging In Neurosurgery

Review Type: Article

Category: Adult Neurosurgery

Journal: Neurosurgery, Vol: 46, No. 5: pages 1112-1122, May 2000

Authors: Wirtz, CR et al

Summary: These authors evaluated 97 procedures for supratentorial gliomas with intraoperative MRI . They found that image quality was adequate (good or fair) in 85% of the cases evaluated and that the incidence of residual tumor postoperatively could be reduced from 62% to 33%. They found the expected increase in survival time for patients without residual tumor by post operative MRI.

The authors acknowledge that the ability to look for residual tumor intraoperatively may have resulted in MRI evaluation before the aggressive gross total resection which would otherwise have been pursued had been completed. This would, of course, have skewed results toward a more significant difference in reduction.

The authors also determined that neuronavigation alone is not sufficient to significantly reduce the rate of residual.

This and other similar studies are necessary to determine the current and future role of this technology in neuro-oncology.

Select Review in Neuro-Oncology

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Volume: 2, Issue: 1

Title: Radiosurgical Salvage Therapy for Patients Presenting with Recurrence of Metastatic Disease to the Brain

Review Type: Article

Category: Adult Neurosurgery

Journal: Neurosurgery, Vol: 46, No. 4: pages 860-867, April 2000

Authors: Chen JCT et al

Summary: This is a retrospective study, which evaluates the use of additional radiosurgery as a salvage method for metastatic disease (with or without whole brain irradiation) (WBI).

Of 190 patients undergoing gamma unit radiosurgery for metastatic brain lesions, 45 also received one or more additional radiosurgical interventions for new lesions arising in regions remote from the previously treated lesion.

The authors found that additional radiosurgery resulted in similar survival times (survival from time of additional treatment) to those produced by initial radiosurgery (survival from time of treatment). Patients undergoing WBI were less likely to require radiosurgical salvage but the overall survival times of the patients treated with WBI vs. those treated with radiosurgery alone (with additional radiosurgery if needed) was similar. 94 of 190 patients did not require or receive either WBI or radiosurgical salvage.

The authors conclude that salvage radiosurgery is a viable and efficacious option for treatment of new metastatic lesions with or without WBI. With salvage radiosurgery as an option, the use of WBI to prevent remote disease must be weighed against the real or potential risk of cognitive decline following WBI.

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Volume: 2, Issue: 1

Title: Glioma Immunology and Immunotherapy

Review Type: Article

Category: Adult Neurosurgery

Journal: Neurosurgery, Vol: 46, No. 4: pages 778-792, April

Authors: Parney,IF et al

Summary: The authors present an excellent review of the current state of immunotherapy as it applies to the treatment of gliomas. Strategies described include vaccination with autologous tumor cells genetically modified to enhance their immunogenicity, local (intratumoral) immunogene therapy and dendritic cell manipulation. A number of pre-clinical trials have yielded promising results and Phase I studies are underway but incomplete.

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Volume: 2, Issue: 1

Title: Long-term follow-up of progesterone receptor status in benign meningioma: a prognostic indicator of recurrence?

Review Type: Article

Category: Adult Neurosurgery

Journal: Journal of Neurosurgery, Vol: 92, No. 3: pages 401-405, Mar. 2000

Authors: Fewings PE, Battersby RDE, Timperley WR

Summary: This paper reports the results of a retrospective review of progesterone receptor (PR) status and meningioma recurrence in long term follow-up of 53 patients. There were a total of 62 tumors, 60 of which were benign. The patients were operated between 1983 and 1985 and follow-up was done in 1997. Patients harboring 14 of the 60 benign tumors were lost to follow-up. Of the 46 tumors in the final analysis, 30% occurred in men and 70% in women and 13 were recurrent, and 33 were non-recurrent. Eleven of the 13 recurrent tumors were PR negative ($P=0.13$). Recurrence was not significantly related to sex, extent of resection, histologic subtype or site. The authors pointed out that the sensitivity and specificity of PR levels as a predictor of recurrence was only 85% and 45%, respectively. The presence of PRs in breast cancer has been shown to convey a more favorable prognosis. Yet meningioma recurrences in this study occurred in 2 of 18 PR positive tumors, indicating that other factors are involved. The authors concluded that PR status and its relationship to other receptors/growth factors deserves further study.

Select Review in Neuro-Oncology

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

Volume: 2, Issue: 1

Title: Treatment of Progressive or recurrent pediatric malignant supratentorial brain tumors with herpes simplex virus thymidine kinase gene vector-producer cells followed by intravenous ganciclovir administration

Review Type: Article

Category: Adult Neurosurgery

Journal: Journal of Neurosurgery, Vol: 92, No. 2: pages 249-254, Feb. 2000

Authors: Packer RJ, Raffel C, Villablanca JG et al.

Summary: This paper reports the results of a multicenter Phase I trial of retroviral HSV-Tk1 and ganciclovir therapy in 12 children with recurrent malignant supratentorial brain tumors. This report follows previous experience with adult patients using the same vector producing system and HSV-Tk1 construct. The G1Tk1SvNa.7 retroviral vector is derived from the Moloney murine leukemia virus and transfers to tumor cells DNA the Tk1 gene which promotes phosphorylation of ganciclovir, which in turn inhibits DNA polymerase. In this protocol 10 ml. of vector producing cells (VPCs) were injected into the walls of the resection cavity and 14 days later ganciclovir was administered at 5mg/kg twice a day for 14 days. An MRI at Day 28 of treatment was used as a baseline. To evaluate for replication competent retrovirus (RCR) peripheral blood was obtained at 1,2, 3, 7, 9 and 12 months to look for antibodies to RCR and the presence of RCR via DNA PCR analysis of peripheral blood leukocytes. The median tumor volume prior to resection was 4.5 cc. (range 0.85-90 cc.).

Four patients (33%) experienced toxicity : one had a seizure and new onset weakness (transient); one had headache, nausea, vomiting and increased weakness (transient); one had a seizure and cerebral edema responsive to steroids (transient) and; one has a seizure, fever and cerebral edema (transient). Twenty-five percent (3/12) of patients had increased enhancement on the baseline scan. Ten of eleven patients had progression at median 5 months after treatment. One patient was alive without disease at 24 months. None of the 50 post treatment blood samples showed evidence of RCR and in none of the 12 patients was there evidence of antibody to the retroviral p30 protein. Viral DNA sequences were detected in 21 of 52 blood samples from 8 patients, but none had a systemic illness. Only one of five patients, whose recurrent tumor was reoperated on some date after the initial injection, showed evidence of RCR by PCR in the recurrent tumor specimen and this result was seen 6 months after treatment.

These results, the authors concluded, demonstrate that in vivo gene therapy can be performed with satisfactory safety and that given the prognosis in these patients further studies were warranted.

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

Volume: 2, Issue: 1

Title: Microanatomical variations in the cerebellopontine angle associated with vestibular schwannomas (acoustic neuromas): a retrospective study of 1006 consecutive cases.

Review Type: Article

Category: Adult Neurosurgery

Journal: Journal of Neurosurgery, Vol: 92, No. 1: pages 70-78, Jan. 2000

Authors: Sampath P, Rini D, Long DM

Summary: The authors review the surgical experience of one surgeon (DML) over a 29 year period to identify the anatomic variations of nerves and arteries in the CPA with specific reference to 8th nerve tumors. Sixty one percent (609) of the tumors were less than 2.5 cm. (Group I); 24%(244)were between 2.5 and 4.0 cm. (Group II) and; 15% (153) were larger than 4.0 cm (Group III). Excluding those operated on via the middle fossa approach (16), 69% were operated retrosigmoid and 29% via a translabyrinthine route. Regardless of tumor size, the facial nerve was located most often on the anterior middle third of the tumor capsule. In only 3.4% of cases did the nerve travel through the substance of the tumor itself. The cochlear nerve was located most commonly on the anterior inferior segment of the tumor capsule, regardless of tumor size. For Group II and III tumors the 5th nerve was involved with the tumor capsule in 90.6% and 100% of cases. For Group II and III tumors the IX-XI complex was involved in 39.8% and 98.7% of cases. Importantly the authors note that with the largest tumors in Group III, involvement of the main trunk or branches of AICA and PICA are especially common (AICA 92-100% ; PICA 59.5-79.1%)and surgeons need to preserve arterial branches within the arachnoid draped over the surface of these large tumors. For example, interruption of the labyrinthine artery, which is a branch off of AICA supplies the meatal and temporal segments of the facial nerve, can lead to permanent severe facial nerve dysfunction.

The authors conclude that for neurosurgeons and neurootologists operating for these tumors, a thorough understanding of the anatomic variation of neural and vascular structures associated with vestibular schwannomas is the key to surgical success. Review of this article is a must for surgeons in training.

Select Review in Neuro-Oncology

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

Volume: 2, Issue: 1

Title: Long-Term Outcome and Growth Rate of Subtotally Resected Petroclival Meningiomas: Experience with 38 Cases.

Review Type: Article

Category: Adult Neurosurgery

Journal: Neurosurgery, Vol: 46, No. 3: pages 567-575, March 2000

Authors: Jun H-W, Yoo H, Paek SH, and Choi KS.

Summary: Resection of large petroclival meningiomas remains a considerable surgical challenge often associated with considerable morbidity. The outcome of subtotal resection as a management strategy has not been well evaluated. The authors present a retrospective analysis of 38 patients who underwent subtotal resection of these tumors with median follow-up of 30 months. The residual neoplasms grew 4.9 cc/yr with a mean doubling time of about 8 years. Growth rate, however, was significantly slower in patients over 50 years of age. The overall progression rate was 42 % with a mean time to progression of 3 years. Based on their findings, the authors suggest that subtotal resection followed by post-operative radiotherapy is a reasonable management strategy for patients with these tumors if they are over age 50, or are at high risk of suffering deficit with complete resection.

Select Review in Neuro-Oncology

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

Volume: 2, Issue: 1

Title: Long Term Outcomes for Surgically Resected Craniopharyngiomas

Review Type: Article

Category: Adult Neurosurgery

Journal: Neurosurgery, Vol: 46, No. 2: pages 291-305, March 2000

Authors: Duff J, Meyer F, Ilstrup D, Laws E, Schleck C, and Scheithauer B.

Summary: Craniopharyngiomas are one of the more common benign neoplasms of the brain, but management remains controversial. Moreover, most published series focus mainly on post-operative results, rather than long term outcome.

This paper represents a retrospective analysis of 121 patients with craniopharyngiomas treated at the Mayo clinic 1974-1991 with median follow-up of 10 years. Unlike most other published series, the authors focused not only on neurologic status and radiologic assessment, but on long term outcome with an emphasis on neurobehavioral assessment.

In their detailed analysis, the authors defined what they considered necessary component of "overall outcome" and assessed the relationships between this and its components such as recurrence, visual function, neurological outcome, functional outcome, and neurobehavioral outcome. After consideration of all these factors, they found that only 60.3% had good "overall outcome." The authors confirmed previous observations that gross total resection was associated with good outcome, and post-operative radiotherapy decreased recurrence. Surprisingly, they also found that age at presentation, and histologic subtypes (ie papillary and adamantinous) were unrelated to outcome. Stable endocrinopathy with hormonal replacement did not necessarily lead to poor outcome.

Select Review in Neuro-Oncology

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

Volume: 2, Issue: 1

Title: A Preliminary Study of the Prognostic Value of Proton Magnetic Resonance Spectrographic Imaging in Gamma Knife Radiosurgery of Recurrent Malignant Gliomas.

Review Type: Article

Category: Adult Neurosurgery

Journal: Neurosurgery, Vol: 46, No. 2: pages 319-328, February 2000

Authors: Graves, E, Nelson S, Vigneron D, Chin C, Verhey L, McDermott M, Larson D, Sneed P, Chang S, Prados M, Lamborn K, Dillon W.

Summary: Stereotactic radiosurgery has been shown to benefit some patients with malignant gliomas in the adjuvant setting. Not surprisingly, patients with smaller tumors have tended to benefit most from this focal treatment. In the setting of recurrent disease however, "size" is difficult to assess with conventional imaging techniques due to the presence of scar and radiation necrosis. The authors have retrospectively applied proton MRI spectroscopy obtained at the time of treatment attempt to identify prognostic indicators for this patient population. They found that patients with spectral abnormalities extending outside the radiosurgical "target," had significantly shorter time to recurrence and survival than those with more focal disease. The contribution that size of the enhancing lesion contributes is unclear. Nonetheless, these findings suggest that MRI spectroscopy may be beneficial in selection of patients for adjuvant radiosurgery as well as in targeting treatment volumes.

Select Review in Neuro-Oncology

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

Volume: 2, Issue: 1

Title: Permanent Iodine 125 Interstitial Implants for the Treatment of Recurrent Glioblastoma Multiforme

Review Type: Article

Category: Adult Neurosurgery

Journal: Neurosurgery, Vol: 46, No. 5: pages 1123-1130, May 2000

Authors: Patel S et al

Summary: This is a retrospective evaluation of 40 patients with recurrent GBM who underwent maximal resection followed by implantation of low dose (total dose of 120 to 160 Gy) iodine 125 implants into the resection cavity intraoperatively.

The authors found that survival was comparable to that achieved with temporary high dose brachytherapy but without the morbidity of radiation necrosis. Age of less than 60 years, gross total resection and a low MIB-1 staining index were associated with longer survival.

Select Review in Neuro-Oncology

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

Volume: 2, Issue: 1

Title: Identification of a Human Glioma-associated Growth Factor Gene, granulin, Using Differential Immuno-absorption

Review Type: Article

Category: Basic Science

Journal: Cancer Research, Vol: 60, No. 5: pages 1353-1360, March 1,2000

Authors: Liao, L.M., Lallone, R.L., Seitz, R.S., Buznikov, A., Gregg, J.P., Korblum, H.I., Nelson, S.F. and Bronstein, J.M.

Summary: There are two aspects of interest in this paper: the approach taken to isolating differentially expressed molecules, and the finding that granulin is a glioma associated protein.

The technique of differential immuno-absorption relies on the creation of a pool of antibodies that is specific to tumor antigens. Antibodies against a glioblastoma multiforme homegenate were raised in rabbits, and purified by positive selection on a GBM-affinity column followed by negative selection on a normal brain affinity column. These columns were made by cross-linking protein extract to a resin, in a standard procedure. The resulting antibodies were then used to screen an expression cDNA library made from GBM, and led to the isolation of 9 known and 9 novel sequences that were differentially expressed.

One of the known genes that was identified as being associated with glioma by this approach, was granulin, which encodes a protein with structural similarity to epidermal growth factor. Northern and in-situ hybridization analysis showed that it is indeed differentially expressed, showing up to 10 fold higher levels in tumor cells than normal glia. This finding is followed up by studies of normal astrocytes in culture, showing that they can be induced to divide by granulins, and by a demonstration that anti-granulin antibodies can inhibit proliferation of glioma cells.

These data provide good evidence that granulin may be a growth promoting molecule in glioma, and suggest that its pathway may yield useful points of intervention. The possibility that granulin overexpression in glioma is another aspect of perturbations in the EGFR signaling pathway is also intriguing.

Select Review in Neuro-Oncology

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

Volume: 2, Issue: 1

Title: Noxa, a BH3-only member of the Bcl-2 family and candidate mediator of p53-induced apoptosis.

Review Type: Article

Category: Basic Science

Journal: Science, Vol: 288, No. 5468: pages 1053-1058, May 2000

Authors: Oda E, Ohki R, Murasawa H, Nemoto J, Shibue T, Yamashita T, Tokino T, Taniguchi T, Tanaka N

Summary: Loss or inactivation by mutation of the tumor suppressor p53 is involved in a majority of all cancers, brain tumors being no exception. Normal function of p53 blocks tumorigenesis by triggering apoptosis, thereby eliminating damaged or misbehaving cells. At least part of the action elicited by p53 arises through its role as a transcriptional activator of genes propagating programmed cell death

Since interference with any of the key convergence points of the programmed cell death pathway would compromise apoptosis (and support tumorigenesis) the cascade of genes and their functions has gained intense attention. Oda et al fill a long-standing gap in the list of p53-responsive mediators of apoptosis in their discovery (using messenger RNA differential display) of a p53 induced gene, Noxa, which induces apoptosis. Thorough biochemical and functional studies of Noxa are elegantly and succinctly depicted

p53-dependent apoptosis occurs by transactivation of Bax, which causes loss of mitochondrial membrane potential. Bax-deficient cells, nonetheless, can undergo p53-dependent apoptosis. Noxa is shown to be transactivated by p53, contains a p53-responsive element in its promoter region, and induces apoptosis when transfected into target cells. By sequence homology Noxa is a member of the Bcl-2 family, but containing only two 9-amino acid sequences characteristic to the Bcl-2 homology 3 (BH3) motif. Immunoprecipitation studies demonstrate that Noxa binds to Bcl-2, essentially quenching the anti-apoptotic activity of Bcl-2

Discovery of the gene repertoire activated by p53, allowing a more accurate assessment of its function as a tumor suppressor gene, is certain to boost our understanding of the molecular pathology of tumors, and offer strategies for development of new therapies.

Select Review in Neuro-Oncology

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

Volume: 2, Issue: 1

Title: TrkC expression predicts good clinical outcome in primitive neuroectodermal brain tumors.

Review Type: Article

Category: Medical Oncology

Journal: Journal of Clinical Oncology, Vol: 18, No. 5: pages 1027-35, March 2000

Authors: Grotzer M, Janss A, Fung K, et al.

Summary: The authors evaluated primitive neuroectodermal tumors (PNET) from 87 children taken from a single institution database. The selection of tumors was based histologic assessment and on the availability of enough tumor tissue to perform in situ hybridization analysis. Patient characteristics can be summarized as follows: Age at diagnosis - <3 yrs 23 (26%), \geq 3 yrs 64 (74%) [median age for all cases 6.5 yrs]; Metastatic stage - M1-3 - 64 (74%), M0 - 20 (23%); Tumor location - Cerebellar 81 (93%), Supratentorial 6 (7%); Surgery - Gross total - 64 (74%), Subtotal - 23 (26%); Therapy - XRT \geq 50 Gy + chemo - 62 (71%), XRT \geq 50 Gy alone - 14 (16%), Chemotherapy alone - 10 (11%); TrkC expression, antisense/sense <1.7 - 35 (40%), \geq 1.7 52 (60%).

TrkC in situ hybridization was performed on paraffin sections cut from formalin-fixed blocks of PNET tissue. High expression of TrkC mRNA in neoplastic cells was identified by in situ hybridization in 52/87 PNETs. Fifty of 81 posterior fossa PNETs and 3 of 6 supratentorial PNETs had high TrkC mRNA expression. Cox regression analysis confirmed significantly greater risks of progression and death associated with metastatic stages M1 to 3 and expression of glial differentiation marker. However, the expression of TrkC mRNA correlated strongly and independently with survival and progression-free survival. The 5 year cumulative-survival rate of the group with a high level of TrkC mRNA expression was 89%, whereas that of the group with a low level of TrkC mRNA expression was 46% ($p=0.00005$). In children younger than 3 years at diagnosis, the expression of TrkC mRNA correlated with survival outcome: the 5-year cumulative survival rate of the group with high level of TrkC mRNA expression was 93%, vs low level TrkC mRNA of 0%.

The exact function of the expression of TrkC remains to be elucidated - perhaps expression confers susceptibility to apoptosis or terminal neuronal differentiation. Regardless, the level of TrkC mRNA expression is the most robust single independent prognostic factor yet identified. Combined evaluation for TrkC mRNA expression and M stage clearly defines a high risk group (TrkC low, M stage \geq 1), an intermediate group (TrkC low, M stage 0), and a group with favorable outcome (TrkC high, any M stage). Incorporation of TrkC mRNA levels will be incorporated into future PNET clinical trials as a key prognostic indicator from this point forward. Another up and coming discriminating factor will be the deliniation of PNETs with rhabdoid differentiation.

Select Review in Neuro-Oncology

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

Volume: 2, Issue: 1

Title: Therapy for patients with high grade astrocytoma using intraarterial chemotherapy and radiation therapy.

Review Type: Article

Category: Medical Oncology

Journal: Cancer, Vol: 88, No. 10: pages 2350-6, May 15, 2000

Authors: Madajewicz S, Chowhan N, Tfayli A, et al.

Summary: The authors report their experience with 83 patients (pts) with malignant gliomas (glioblastoma multiforme [GBM] n = 63; anaplastic astrocytoma [AA] n = 20) who received intraarterial (IA) chemotherapy (CTX) and radiation therapy (RT). One group received two to three courses of IA CTX prior to radiation and the other received three courses of IA CTX concomitantly with RT. Overall, 12 pts (14%) underwent complete resection, 27 (32%) pts underwent partial resection, and 44 pts had biopsy only. The Karnofsky Performance Status (KPS) of 56 pts (67%) was below 70 with 49 of these pts having GBM.

Premedication was with IV dexamethasone and methylprednisolone. The catheter tip was advanced to the appropriate internal carotid or vertebral artery. The cytotoxic agents used were combination cisplatin (60 mg/m²) and etoposide (40 mg/m²). RT was administered within 2 weeks after the last course of IA CTX for pts in the first group. The group treated with concomitant RT had the RT initiated within a week of the first IA infusion.

Forty-three pts were evaluable for neoadjuvant IA CTX (34 GBM, 9 AA). In this group, there were 4 complete radiographic responses ([CR] 9%), and 20 partial responses ([PR] 47%) after chemotherapy alone. Pts with GBM experienced a median survival of 20 months whereas pts with AA had a median survival of 45 months. Twenty-eight pts were evaluable for the concomitant RT + CTX group (22 GBM, 6 AA). Ten PR's were observed. Median survivals of 7 months for GBM and 12 months for AA pts were noted, approximately 3 times less than the neoadjuvant group.

While it is certainly not appropriate to make broad, sweeping changes in chemotherapy administration based on the results of 71 evaluable pts with differing histologies (GBM,AA), the results of this study are nevertheless encouraging. The neoadjuvant administration of CTX has been repeatedly shown to be safe and effective to varying degrees. The dosages used in this study are on the low side, and the techniques of super-selective catheterization or blood brain barrier disruption were not utilized. Our own institution doses based on cerebral blood flow (not body surface area) as described by the UCLA group, allowing for the safe administration of higher doses. Other chemotherapy agents may be used alone or in combination. The primary CNS lymphoma literature has demonstrated convincingly that repeated cycles of neoadjuvant IA CTX administration is both safe and effective in that disease setting. Clearly, an experienced interventional neuroradiologist is needed for maximum benefit to the patient.

Select Review in Neuro-Oncology

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

Volume: 2, Issue: 1

Title: Preliminary individual adjuvant therapy for gliomas based on the results of molecular biological analyses for drug-resistance gene

Review Type: Article

Category: Medical Oncology

Journal: Journal of Neuro-Oncology, Vol: 46, No. : pages 157-171, 2000

Authors: Tanaka S, Kamitani H, Armin MR, Watanabe T, Oka H, Fujii K, Nagashima T, Hori T

Summary: In this report the authors used molecular techniques to correlate candidate drug resistance genes in glial tumors with in vitro and clinical responses to chemotherapy, then used the results to direct use and choice of chemotherapy in a preliminary clinical trial. Reverse transcriptase polymerase chain reaction (RT-PCR) was used to assay for multidrug-resistance gene 1 (MDR1), multidrug-resistance-associated protein (MRP), glutathion-S-transferase-pi (GST-pi) and O6-methylguanine DNA methyl-transferase (MGMT). In cell lines resistant to ACNU, vincristine, or cis-platinum, there was expression of MGMT, MDR1 & MRP, or GST-p, respectively. In evaluation of 23 patients previously treated with ACNU, clinical response was highly associated with lack of MGMT mRNA expression ($p=0.0037$ by multivariate analysis).

Buoyed by these results, a clinical trial was undertaken in 1997 where the results of RT-PCR was used to direct use of chemotherapy in 30 patients (37 courses of treatment -- 21 at initial diagnosis and 16 at recurrence). In general, ACNU was used in MGMT-negative cases, while cis-platinum or carboplatin was used in MGMT-positive cases. Unfortunately, the types of tumors treated were broad (glioblastoma, anaplastic astrocytoma, oligodendroglioma, astroblastoma, pineoblastoma and medulloblastoma) and other therapies were also used (often interferon-b). The authors cite a 56% overall good response (CR or PR) rate and 41.7% for GBM. Interestingly, when looking only at the 8 of 11 glioblastoma patients that were MGMT negative, the response rate to ACNU (CR, PR, stable disease) was 50% - probably better than expected, but far from a highly predictive test. As such, this is an interesting approach to titrating adjuvant chemotherapy and deserves further evaluation.

Select Review in Neuro-Oncology

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

Volume: 2, Issue: 1

Title: Boswellic acids inhibit glioma growth: a new treatment option?

Review Type: Article

Category: Medical Oncology

Journal: Journal of Neuro-Oncology, Vol: 46, No. : pages 97-103, 2000

Authors: Winking M, Rahmanian A, Jodicke A, Boker DK

Summary: The gum resin of *Boswellia serrata* is known for potent anti-inflammatory properties and has been shown to reduce peritumoral edema and improve clinical condition in patients with glioblastoma. It is thought that these boswellic acids inhibit 5-lipoxygenase, and therefore reduce products in its metabolic pathways such as cysteinyl-LT. As gliomas tend to produce cys-LT (which stimulates glioma cell proliferation) the authors hypothesize use of boswellic acids may inhibit glioma growth.

A C6 glioma model was used in female Wistar rats. Animals were treated in two arms - one that gave BA (60, 120 or 240 mg/kg) before tumor implantation, the other in animals with pre-existing tumors. Results were assessed on the basis of tumor volume, apoptosis and clinical condition of the animals. Dose dependent inhibition of tumor growth ($p < 0.05$) and, accentuation of apoptosis was found in the animals implanted after pre-treatment with BA ($p < 0.05$). In the animals treated after 14 days of tumor growth, survival was doubled as compared to controls ($P < 0.05$). Hair loss was observed to be the only adverse effect of high dose treatment.

Historically, extracts from plants have proved to be fertile sources of pharmaceuticals, including chemotherapeutic agents such as paclitaxel (Taxol) which is extracted from the bark of the western yew. It should not then be a foreign notion that other plant extracts may have favorable effects on brain tumors. Further characterization and purification of the active constituents of the Boswellic acids may serve as both new approaches to the treatment of brain edema, and to the tumor itself.

Select Review in Neuro-Oncology

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

Volume: 2, Issue: 1

Title: Long-term outcome of low-grade oligodendroglioma and mixed glioma.

Review Type: Article

Category: Medical Oncology

Journal: Neurology, Vol: 54, No. 7: pages 1442-8, April 11, 2000

Authors: Olson JD, Riedel E, DeAngelis LM.

Summary: The authors provide a single institution retrospective review of 106 patients with low-grade oligodendroglioma (n=77) and low-grade mixed glioma (n=29). This group was selected to clarify issues of timing and effectiveness of radiation therapy (RT) and chemotherapy (CTX) with respect to patient management. Presenting symptoms were seizures in 76 (72%), headache in 11 (10%), and cognitive disturbance in 6 (6%) of patients. The median age of presentation was 37 years of age. Remarkably, the median time from symptom onset to diagnosis was only 18 days, reflecting an 8 month to 3 year lead time bias (mostly due to advanced neuroimaging techniques). Surgery at initial diagnosis consisted of biopsy in 28, subtotal resection in 41, and gross total resection in 19. Initial treatment selection was observation in 68, RT in 20, CTX in 12, and RT + CTX in 6. RT was eventually administered to 62 patients and CTX to 76 patients.

The median time to progression (MTTP) from initial diagnosis for all 106 patients was 5.0 years. Tumor recurrence was histologically confirmed as anaplastic or high grade in 35 and low grade in 20; no pathologic confirmation at recurrence was obtained in 17 patients. MTTP was 5.7 years after post-operative RT and not reached after initial treatment with CTX. Patients treated with RT + CTX had MTTP of 8.6 years. Only 19 patients died during the study (patients diagnosed between 1979 and 1997) with median overall survival of 13.5 years in pathology confirmed cases.

Radiation necrosis was diagnosed in 9 (15%) patients a median of 52 months following RT. Cognitive decline as a result of RT occurred in 13 (21%) of patients. The use of higher dose of 'up front' RT in this study extends the EORTC data on low-grade gliomas, suggesting strongly that when RT is used/indicated for treatment, moderate doses (45-50 Gy) are just as effective and impart fewer side effects. Significant myelosuppression from chemotherapy (PCV was the most frequently used regimen) occurred in 35 (46%) of patients. Procarbazine rash occurred in 15, herpetic rash in 10, and pulmonary toxicity in 4 patients.

There were no apparent differences in either immediate versus deferred treatment or choice of initial therapy on disease-free or overall survival. Furthermore, there were no statistically significant differences for age, histologic diagnosis, extent of resection or enhancement on time to progression or overall survival. However, one limitation of this review was that very few patients died and these data may not have had sufficient power to detect the impact of these factors on outcome. Chemotherapy (mostly PCV) was associated with significant acute toxicity in almost one half of patients; radiation therapy produced late neurotoxicity in one third, justifying deferred treatment until clinically necessary based on treatments available in the time frame studied.

This study, although not a prospective analysis, addresses several items of contention in the treatment of low-grade oligo-containing tumors. It is a key reference for patient management but not an all-inclusive algorithm. Two advances now available that may alter plans for therapy include the chemosensitivity of low grade oligo-containing tumors with 1p/19q allelic loss and the advent of cytotoxic drugs with more favorable therapeutic indices such as temozolomide. Cases should be treated individually, using all tools available to aid best clinical judgement.

Select Review in Neuro-Oncology

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

Volume: 2, Issue: 1

Title: Treatment of Optic Nerve Sheath Meningioma With Three-Dimensional Conformal Radiation

Review Type: Article

Category: Neuro-Ophthalmology

Journal: American Journal of Ophthalmology, Vol: 129, No. 5: pages 694-696, May 2000

Authors: Moyer PD, Golnik KC, Breneman J

Summary: This is a case report of a 35-year-old female who noted blurred vision. Exam disclosed visual acuity of 20/200 in the affected eye and an afferent pupillary defect. There was moderate generalized ophthalmoplegia and 3-mm of proptosis. The optic nerve head was mildly swollen. Visual field testing showed a central defect with some inferior and superior field loss. Magnetic resonance imaging disclosed a 1.8-cm x 1.8-cm x 1.2-cm lesion surrounding the optic nerve, and having characteristics consistent with optic nerve sheath meningioma. The patient received radiation (28-180 cGy fractions, 5040 cGy total, over 42 days) administered by a three-dimensional conformal technique, wherein six beams of radiation were aimed and shaped by passing through an aperture in a radio-opaque alloy block, whose size and shape was specified by a computer. One month later, the visual acuity had improved to 20/40, the visual field defect had nearly resolved, the optic nerve head swelling had resolved, but the proptosis and ophthalmoplegia had not improved. MR imaging at 8 months showed a slight decrease in tumor size.

This report demonstrates the usefulness of three-dimensional conformal radiation over conventional radiotherapy in helping to limit damage to surrounding normal tissue, especially the contralateral optic nerve, retina, lens, and frontal lobe of the brain.

References: Lee AG, Woo SY, Miller NR, et al. Improvement in visual function in an eye with a presumed optic nerve sheath meningioma after treatment with three-dimensional conformal radiation therapy. *Journal of Neuro-ophthalmology*. 1996;16:247-251.

Select Review in Neuro-Oncology

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

Volume: 2, Issue: 1

Title: Pineal parenchymal tumors: A correlation of histological features with prognosis in 66 cases

Review Type: Article

Category: Neuro-Pathology

Journal: Brain Pathology, Vol: 10, No. 1: pages 49-60, Jan 2000

Authors: Jouver A, Saint-Pierre G, Fauchon F, et al

Summary: This large series is particularly notable for providing prognostic information for the group of "intermediate" differentiation pineal parenchymal tumors. 66 pineal parenchymal tumors (PPT) including pineocytoma(PC,11), pineoblastoma(PB,16), and intermediate/mixed(IPPT,39) were reported with clinical, morphologic, and immunohistologic data. Some of the IPPT group including 9 "transitional" type cases may be classified as pineocytomas by some neuropathologists. A mixture of typical PC and PB was rarely seen (2 cases). Within all PPTs, statistically significant factors in overall survival and event free survival were: Morphologic subtype (pineocytoma or pineoblastoma), mitotic activity, necrosis, neurofilament immunostaining (70/200 KDa, Dako 2F11), and a proposed new 4 grade system that used those criteria. The proposed grading system divided PPTs into pineocytoma (grade I), 2 grades of intermediate PPT (grades II and III), and pineoblastoma (grade IV). IPPT were divided into those with detected neurofilament and mitotic rate less than 6 per 10 400x fields (field area not provided), and those that were either negative for neurofilament or had mitotic rate greater than 6 per 10 400x fields (grade III). Median follow-up was 3.5 yrs (0-21 yrs). PC was the most favorable group, with no deaths beyond the perioperative period. PB was least favorable with downward survival curve and no survivors at 45 months. Grade II and III IPPTs had distinct survival curves lying between PC and PB. This large series confirms age distribution of these tumors, with PC occurring in older group (10-65 yrs) than PB (1-36 yrs).

Select Review in Neuro-Oncology

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

Volume: 2, Issue: 1

Title: Comprehensive allelotype and genetic analysis of 466 human nervous system tumors

Review Type: Article

Category: Neuro-Pathology

Journal: Journal of Neuropathology and Experimental Neurology, Vol: 59, No. 6: pages 544-558, June, 2000

Authors: von Deimling A, Fimmers R, Schmidt MS, et al

Summary: If a large amount of genetic data obtained from a wide variety of nervous system neoplasms is of interest to you, then this article should be in your files. One must appreciate the amount of aggregate labor involved in collecting, analyzing, and reporting this information on such a large group of neoplasms. The genetic information includes data based on loss of heterozygosity studies with 129 microsatellite markers, PCR analyses for amplification of EGFR and CDK4 and for deletions of CDKN2A, PTEN, and DMBT1, and SSCP with direct sequencing analyses for TP53, PTEN, and NF2 gene mutations. The 466 tumors analyzed included a variety of neoplasms, some have been previously relatively extensively studied while others have not. Among the data are findings that support previously reported genetic differences in primary and secondary GBMs, for example TP53 mutation and EGFR amplification seem mutually exclusive. Oligodendrogliomas (grades I and II) showed a low frequency of TP53 mutations (5%) and more frequent LOH on 1p (47%) and 19q (71%). While the frequency of LOH on 1p and 19q was similar, oligoastrocytomas showed more frequent TP53 mutation (37%) compared to oligodendroglioma. Aside from these examples, there are data obtained from pilocytic astrocytomas (29 cases), pleomorphic xanthoastrocytoma (4), ependymoma and anaplastic ependymoma (10), ganglioglioma and anaplastic ganglioglioma (16), hemangiopericytoma (4), central neurocytoma (2), meningioma and anaplastic meningioma (84), among many others.

Select Review in Neuro-Oncology

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

Volume: 2, Issue: 1

Title: Neuropsychological consequences of cerebellar tumour resection in children: Cerebellar cognitive affective syndrome in a pediatric population.

Review Type: Article

Category: Neuropsychology

Journal: Brain, Vol: 123, No. : pages 1041-1050, 2000

Authors: Levisohn, L. , Cronin-Golomb, A., & Schmahmann, J.D.

Summary: The Authors utilize a series of children treated for cerebellar tumours of the vermis, deep nuclei and hemispheres according to blind review of the postoperative MRI. Subjects included 19 children, 11 with medulloblastom, 7 with astrcytoma, and 1 ependymoma, ranging in age from 3 years 3 months to 14 years 10 months (mean=8 years 2 months). In order to limit conclusions to the effects of tumour alone, no participants had been exposed to cranial radiation or methotrexate prior to testing, as each has a known association with cognitive decline; their exclusion criteria allowed for treatment with cisplatin, CCNU, glycoposphamide, and vincristine, as cognitive complications from these agents appears less probable.

Patients were tested within 2 years of surgery. Neuropsychological tests were solid choices, covering intelligence and expectable basic cognitive domains. All tests are readily available, providing for easy study replication. The study designation of 1.5 SD below the mean to represent a significant deficit is quite reasonable. Using 1.0 SD can result in excessive false positives; the more conservative criterion of 2.0 SD is often too restrictive.

Findings in this paper nicely parallel those evident in the adult literature regarding a cerebellar cognitive affective syndrome. In a statistic easily derived from stated information but unreported in the paper, 58% of these patients (11/19) demonstrated some type of cognitive deficit. Beyond the expected pure motor findings (e.g., impaired dexterity in 14/19 patients), tumors of the cerebellar hemispheres were associated with cognitive disturbance in the areas of language, visuospatial skill, sequencing, memory, and affect regulation. In contrast to this hemispheric influence , lesions of vermis were associated with affective behavioral disturbance (all those with affective disturbance had "extensive vermis damage;" none of those without affective disturbance had similar damage to the vermis).

In this series, younger patients were less likely to show formal cognitive deficits, while older patients demonstrated cognitive dysfunction more prominently (deficits in 3/9 patients < 7 years, but in 8/10 patients > 7 years). However, this apparent effect of age at the time of surgery was directly confounded by tumour type: Medulloblastoma was uncommon in younger children (4/11) while astrocytoma was uncommon in older children (2/7). Thus, the relative contributions of age vs tumour type remain vague. Other contributing factors posited to account for fewer deficits in younger children include greater neuronal plasticity in those younger, and the matter of "growing into a deficit" - the fact that by normal development, only older children can expectably demonstrate a deficit in organizational and abstraction skills. The authors appropriately comment that longitudinal follow-up of these children is required to examine the permanence of the deficits they found. They also recognize that a larger sample size would assist in identifying possible hemispheric asymmetries in cognitive mediation.

References: B.E Connell, Ph.D.

Select Review in Neuro-Oncology

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

Volume: 2, Issue: 1

Title: Comparison of Patient Age with MR Imaging Features of Gangliogliomas

Review Type: Article

Category: Neuro-Radiology

Journal: American Journal of Roentgenology, Vol: 174, No. 3: pages 859-862, Mar 2000

Authors: Provenzale JM, Ali U, Barboriak DP, Kallmes DF, DeLong DM, McLendon RE

Summary: The authors present a study comparing the MR imaging features of proven gangliogliomas in children less than 10 years old (6 pts; mean age 5.5 years) to those in young adults (19 patients; mean age 25.6 years). They found no significant differences in tumor location (temporal lobe predominance) or enhancement (5/6 younger patients; 13/16 older patients). Tumor volume was significantly larger in the younger group (83 ccs vs 10 ccs though mitotic indices were similar [all < 1%]), the percentage of cystic change in tumors was larger in the younger group (67% v 30%) though cysts were present in the majority of tumors in both groups (83% in the younger group; 63% in the older group). No outcomes data with respect to these patient groups is presented.

Comment: The authors are unsure as to why younger patients present with much larger tumors though they discuss several possible hypotheses. Otherwise, imaging features (and apparently histologic features) of gangliogliomas are similar in children and young adults.

Select Review in Neuro-Oncology

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

Volume: 2, Issue: 1

Title: Perfusion MR Imaging of Brain Tumors

Review Type: Article

Category: Neuro-Radiology

Journal: American Journal of Roentgenology, Vol: 174, No. 4: pages 1147-1157, Apr 2000

Authors: Wong JC, Provenzale JM, Petrella JR

Summary: After reviewing some of the physics basic to perfusion MR imaging (also called dynamic susceptibility contrast MR imaging), the authors present a pictorial essay demonstrating possible benefits of using perfusion MR to evaluate brain tumors with respect to grading neoplasms, delineating the extent of tumors (e.g. for radiation therapy planning), selecting areas for stereotactic biopsy, and differentiating between radiation necrosis and recurrent tumor. Also presented are examples of the technique failing to detect small areas of recurrent high grade glioma and also failing to differentiate recurrent low grade gliomas from radiation necrosis.

Comment: It is well-known that conventional MR is suboptimal for delineating the true extent of high grade gliomas and is also suboptimal for differentiating between recurrent neoplasm and radiation necrosis as enhancement on MR only reflects breakdown of the blood brain barrier and/or tumor angiogenesis and not the complete extent of a lesion. Increased signal on perfusion MR may better reflect tumor neovascularity which could better delineate a site for stereotactic biopsy (high signal), suggest a tumor grade (higher signal suggests higher grade) or differentiate between radiation necrosis (low signal) and recurrent tumor (high signal). Unlike PET imaging, no special imaging equipment or imaging agents are necessary. Similarly, perfusion MR imaging requires only the appropriate software on standard clinical machines which are already in use.

Therefore, while additional work needs to be done, perfusion MR may very well prove to be a simple method for differentiating recurrent tumor from radiation necrosis and also for delineating areas for stereotactic biopsy.

Select Review in Neuro-Oncology

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

Volume: 2, Issue: 1

Title: Symptomatic Brachial Plexopathy following Treatment for Breast Cancer: Utility of MR Imaging with Surface Coil Techniques

Review Type: Article

Category: Neuro-Radiology

Journal: Radiology, Vol: 214, No. 3: pages 837-842, Mar 2000

Authors: Qayyum A, MacVicar AD, Revell P, Husband JES

Summary: 50 patients with a history of previously treated (surgery, chemotherapy and radiation therapy) breast carcinoma now with symptoms of brachial plexopathy (pain, weakness, parasthesia) underwent high resolution MR imaging using surface coils in an attempt to determine whether spread of cancer or a benign process (e.g. radiation change) was responsible for their respective plexopathies.

26/27 patients with tumor involvement of the brachial plexus were correctly identified by MR; 20/21 patients without spread of neoplasm to the brachial plexus were also correctly diagnosed by MR. The authors found a PPV, NPV, sensitivity and specificity of at least 95% for each when evaluating these patients and conclude that surface coil MR imaging should be the imaging modality of choice for evaluating these patients.

Comment: The authors used identification of a mass as their best criterion for diagnosing spread of neoplasm; they considered diffuse thickening of brachial plexus structures without a focal mass as evidence for radiation plexopathy. Signal changes by themselves (i.e. without an associated mass) were not considered consistent with spread of neoplasm. Of the 27 patients in whom the diagnosis of spread of cancer was made, only 5 had histologic confirmation; other patients were considered positive if lesions progressed over time or responded to therapy.

It is known that carcinoma can diffusely involve the brachial plexus without focal mass formation. This is the basis for performing PET imaging in many of these patients. I'm concerned of the results of this study as a) few patients had histologically confirmed proof of presence/absence of neoplasm and b) the presented positive patients in this paper each had large masses (and I would assume that small metastases to the brachial plexus could cause symptoms also, but would be difficult to demonstrate at imaging). Therefore, until confirmed by other researchers on a more diverse patient group, management of these patients should still not primarily be based on MR imaging.

Select Review in Neuro-Oncology

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

Volume: 2, Issue: 1

Title: Brain Tumor Resection: Intraoperative Monitoring with High Field Strength MR Imaging – Initial Results

Review Type: Article

Category: Neuro-Radiology

Journal: Radiology, Vol: 215, No. 1: pages 221-228, Apr 2000

Authors: Martin AJ, Hall WA, Liu H et al

Summary: 30 patients undergoing brain tumor resection (11 GBMs, 1 anaplastic astrocytoma, 7 low grade gliomas, 3 meningiomas, 2 gangliogliomas, 2 metastases, 1 craniopharyngioma, 1 oligodendroglioma, 1 medulloblastoma, 1 teratoma) were evaluated with pre-operative, intraoperative and post-operative 1.5 T MR imaging. Additional tissue resected as the result of intra-operative imaging underwent separate histologic evaluation.

The authors found that using intra-operative MR imaging resulted in 24/30 patients having all tumor resected at surgery. They also found that areas of enhancement on intraoperative MR images were not specific for residual tumor.

Comment: It makes sense that imaging performed during any surgical procedure is useful/helpful in confirming what has been done, the current appearance of the surgical site, the location of nearby structures that need to be avoided [e.g. vessels] and whether any additional residual tumor needs to be resected. While MR is clearly better than other imaging modalities for demonstrating intracranial pathology, the authors have not shown any benefit of MR over intra-operative ultrasound, a much less expensive, quicker and more easily implemented technology. Also, even if all areas of contrast enhancement are resected, in high grade tumors, this does not mean that all tumor has been resected. Finally, controversy exists regarding the true benefit of more complete resections in the setting of the most common primary malignant CNS tumors.

This preliminary report is not convincing with respect to the value or need for intra-operative MR imaging for brain tumor resection.

Select Review in Neuro-Oncology

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

Volume: 2, Issue: 1

Title: Posttherapeutic intraaxial brain tumor: the value of perfusion-sensitive contrast-enhanced MR-imaging for differentiating tumor recurrence from nonneoplastic contrast-enhancing tissue

Review Type: Article

Category: Neuro-Radiology

Journal: Am J Neuroradiol, Vol: 21, No. : pages 901-909, May 2000

Authors: Sugahara T, Korogi Y, Tomiguchi S, et al

Summary: The authors examined the use of dynamic Gd-enhanced perfusion MR for differentiating tumor recurrence from non-neoplastic enhancing tissue within irradiated tissue. They prospectively studied 20 patients (19 with gliomas of various grades and 1 with a PNET) six to 94 months following diagnosis. Relative cerebral blood volume (rCBV) ratios were calculated for new enhancing lesions. Six cases were histologically proven; etiologies for lesions in the other cases were determined presumptively from follow-up scans. Twelve patients also underwent thallium SPECT brain scanning.

There was a large amount of overlap in the rCBV ratios of tumor recurrence and non-neoplastic enhancing tissue. Arbitrary cut-off values allowed differentiation in only 7 out of 20 cases. Four patients with a rCBV ratio greater than 2.6 had recurrent tumor, and three with ratios less than 0.6 had non-neoplastic tissue. Increased TI uptake suggested recurrent tumor in some patients with rCBV ratios between these values, but this modality was not used in all patients.

These data point out the limited usefulness of MRI perfusion studies in differentiating between tumor and radiation necrosis. This study suffers from a relatively small number of patients, limited statistical analysis, and histologic proof in only a minority of patients. Not all patients underwent thallium scanning, although data regarding TI-SPECT are intriguing.

Select Review in Neuro-Oncology

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

Volume: 2, Issue: 1

Title: Practice parameter: Anticonvulsant prophylaxis in patients with newly diagnosed brain tumors. Report of the Quality Standards Subcommittee of the American Academy of Neurology.

Review Type: Article

Category: Neurology

Journal: Neurology, Vol: 53, No. 10: pages 1886-93, May 23, 2000

Authors: Glantz M, Cole B, Forsyth P, et al.

Summary: Physicians often administer anticonvulsant medication (AEDs) prophylactically to patients with brain tumors, despite the lack of definitive evidence in preventing first seizures. The exposure to these AEDs can result in life threatening adverse events (e.g. Stevens-Johnson syndrome) and can interfere with the metabolism of commonly used cytotoxic agents and steroids. The authors performed a meta-analysis on seizure incidence using all identified prospective, randomized clinical trials and odds ratios (OR) calculated. The available evidence suggests that prophylactic administration of AEDs does not provide substantial benefit. Many patients who experienced seizures while receiving anticonvulsant prophylaxis had subtherapeutic anticonvulsant blood levels although one randomized controlled trial that addressed that issue specifically refutes this consideration.

The recommendations of the Subcommittee were outlined as follows: 1. In patients with newly diagnosed brain tumors, AEDs are not effective in preventing first seizures. Because of their lack of efficacy and their potential side effects, prophylactic AEDs should not be used routinely in patients with newly diagnosed brain tumors. 2. In patients with brain tumors who have not had a seizure, tapering and discontinuing AEDs after the first postoperative week is appropriate, particularly in those patients who are medically stable and who are experiencing AED related side effects.

The authors do point out areas of future research. Perhaps other AEDs with better side effect profiles can be effective. Some subgroups of patients with hemorrhagic lesions and 'high risk' tumors have not been evaluated by prospective randomized trials. There are also some methodological shortcomings to the performance of a meta-analysis that must be considered.

Select Review in Neuro-Oncology

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

Volume: 2, Issue: 1

Title: Cyst wall enhancement in pilocytic astrocytoma: Neoplastic or reactive phenomena

Review Type: Article

Category: Pediatrics/Pediatric Neuro-Oncology

Journal: Pediatric Neurosurgery, Vol: 32, No. : pages 234-239, 2000

Authors: Liana Beni-Adani, MosheGomori, Sergei Spektor and Shlomi Constantini

Summary: The authors prospectively evaluated a small series (n=3) of patients with juvenile pilocytic astrocytoma consisting of a mural nodule and prominently enhancing cyst wall. Intra-operative appearance in each case revealed a clear border separating a benign appearing cyst wall from the tumor nodule. Cyst wall biopsies were negative for tumor and no attempt was made to surgically remove the cyst. Clinical and radiographic follow-up of greater than or equal to 4 years revealed no residual or recurrent disease. The authors review the limited and sometimes incomplete or contradictory evidence in the literature regarding the pathobiology of cyst walls in juvenile pilocytic astrocytoma. Their review and findings suggest that even prominently enhancing cyst walls associated with juvenile pilocytic astrocytoma may not represent tumor. The authors argue against excision of such cyst walls, especially in eloquent areas.

References: Nathan Selden, M.D.

Select Review in Neuro-Oncology

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

Volume: 2, Issue: 1

Title: The Significance of Radiotherapy Treatment Duration in Intracranial Ependymoma

Review Type: Article

Category: Radiation Oncology

Journal: Int. J. Radiation Oncology Biol. Phys., Vol: 47, No. 3: pages 585-589, June, 2000

Authors: Paulino, Ac and Wen,BC

Summary: Radiation treatment duration and treatment interruption has been well documented as having a detrimental effect on tumor control for such sites as head and neck malignancies. More recently, there has been data suggesting the same finding in medulloblastoma (see reference 1 below). This article is a retrospective review of 34 cases of intracranial ependymoma treated with postoperative radiation therapy at the University of Iowa and Children's Hospital of Iowa which seeks to relate local control and survival with duration of treatment. Although subject to the pitfalls of retrospective reviews (which is the only way to evaluate for this type of information since there will never be a trial designed to provide level I evidence for radiation treatment breaks), the data suggests that for patients whose radiation took > 50 days to deliver, outcome was worse as summarized as follows

< 50 day RT duration	>= 50 days RT duration	
5 year survival	85.5 %	45.4 %
10 year survival	78.9 %	36.4 %
15 year survival	65.7 %	36.4 %
10 & 15 year local control	70.6 %	36.4 %

Although the numbers are small, the differences reached statistical significance. There was no effect of age, gender, tumor location, tumor grade, degree of surgical resection, RT volume or RT dose on survival or local control. As might be expected, patients who received craniospinal radiation were more likely to have required a break (9/14) because the large volume of marrow radiated resulted in hematologic toxicity, than patients receiving whole brain or involved field alone (3/20).

Unfortunately, this data is somewhat confounded by the fact that patients treated early in this study (1960's-1980's) were more likely to have been treated with craniospinal RT than patients treated in the 1990's because of a change in treatment philosophy, and it is likely that the patients from the earlier era were not as thoroughly staged for either extent of resection or dissemination, which could result in worse outcome for this group. Nevertheless, the finding is consistent with the radiobiological concept of accelerated regeneration (see reference 2) below, which suggests that there is a potential for increased tumor regeneration at approximately the end of the third or fourth week of conventionally fractionated radiation and that a treatment break during this period of time could result in loss of local control. It would be interesting to evaluate whether the point at which treatment was interrupted was correlated with outcome on this study, but it is likely that the breaks were clustered at the same point in time during the RT which would make the analysis difficult.

References: 1. delCharco, JO, Bolek, TW, McCollough, WM, et al. Medulloblastoma: Time-Dose Relationship Based on a 30-Year Review. Int. J. Radiation Oncology, Biol. Phys., 42(1):147-154, 1998.

2. Withers, HR, Taylor, JMG, Maciejewski, b. The Hazard of Accelerated Tumor Clonogen Repopulation During Radiotherapy. Acta Oncol 27: 131-146, 1988.

Select Review in Neuro-Oncology

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

Volume: 2, Issue: 1

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, Jan 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: 1

Title: Radiosurgery for brain metastases: A score index for predicting prognosis.

Review Type: Article

Category: Radiation Oncology

Journal: International Journal of Radiation Oncology Biology Physics., Vol: 46, No. 5: pages 1155-1161, March 2000

Authors: Weltman E, Salvjoli JV, Brandt RA et al

Summary: This article from Brazil presents a score index for predicting prognosis of brain metastases patients who are treated with radiosurgery. The RTOG published a prognostic system using three classes based on a retrospective analysis of three consecutive RTOG studies of 1200 patients treated with whole brain XRT. Using a recursive partitioning analysis model, three classes were identified. The best prognostic class was defined on the basis of young age, good KPS, controlled primary, and absence of extracranial metastases. The worst class had a KPS<70 and class two was in between. Although this was interesting, Class 1 patients represent a very small subgroup of brain metastases patients and Class 2 is not that helpful in deciding which patients should be considered for radiosurgery.

The Brazilian authors analyzed their experience with 65 brain met patients treated with radiosurgery and followed for over twelve months. They retrospectively determined that the most important factors predicting prognosis was age, KPS, systemic disease status, largest lesion volume, and number of lesions. Each factor was divided into three groups and each group scored from zero to two yielding a score index (SIR) from zero to ten. A ten would indicate a patient with one lesion less than 5 ccs with a KPS >70, <50 years old, and without evidence of systemic disease. The index was divided into three classes with scores of 0-3, 4-7, and 8-10. Median survival for these classes was 3, 7, and 31 months. Using a Cox model, the SIR was an independent predictor of prognosis while RPA was not. There was a good distribution of patients among each index score. Subjectively, the SIR survival curves seemed better separated than using a RPA system. This prognostic system needs to be validated on a much larger database such as the RTOG 95-08 study.

It may turn out that the better prognostic precision could be achieved with fewer variables or different group criteria. Nevertheless, the SIR index is quite simple to use and would be of interest to those trying to decide which patients would benefit from radiosurgery and which patients would be unlikely to suffer long-term neurocognitive toxicity from whole brain radiation therapy.

Combined postoperative irradiation and chemotherapy for anaplastic ependymomas in childhood: Results of the German prospective trials HIT 88/89 and HIT 91. INTERNATIONAL JOURNAL OF RADIATION ONCOLOGY BIOLOGY PHYSICS. Vol. 46, No. 2, pp 287-295, 2000. Timmerman B, Kortmann R-D, Kuhr J, et al. 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.

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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 ependymoblastoma or medulloblastoma. Overall, this study is a valuable addition to the literature on this rare entity

Select Review in Neuro-Oncology

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

Volume: 2, Issue: 1

Title: Single dose radiosurgical treatment of recurrent previously irradiated primary brain tumors and brain metastases: final report of RTOG protocol 90-05

Review Type: Article

Category: Radiation Oncology

Journal: Int J Radiat Oncol Biol Phys, Vol: 47, No. 2: pages 291-8. , May 1, 2000

Authors: Shaw E; Scott C; Souhami L; Dinapoli R; Kline R; Loeffler J; Farnan N

Summary: RTOG 90-05 represents the first multi-institutional study examining dose escalation for radiosurgery. Adults with solitary recurrent cerebral or cerebellar tumors less than 4 cm. in size were eligible. One third had a variety of primary brain tumors and two thirds had brain mets. Doses were escalated by 3 Gy increments until "unacceptable CNS toxicity" was encountered. The maximum tolerated doses were 24 Gy, 18 Gy, and 15 Gy for tumors < 2 cm., 2.1 to 3.0 cm, and 3.1 to 4.0 cm. Larger tumor diameters predicted an increased risk of unacceptable CNS toxicity (tumors 2-3cm and 3-4 cm had odds ratios of 7.3 and 16 increased risk versus <2cm) as did higher KPS. This data is the basis of the dose recommendations in RTOG 93-05 and 95-08. The authors also analyzed factors predicting radiographic tumor control. The authors noted an increased risk of local tumor progression for recurrent primary brain tumors versus brain metastases and for LINAC based radiosurgery versus gamma knife.</p>

<p>This important study demonstrated that a Phase I multi-institutional radiosurgery trial can be properly run to obtain valuable dose tolerance data. Unfortunately, the data has also been improperly used by those advocating the Gamma Knife. The study was not designed with radiographic tumor control as an endpoint- the endpoint was toxicity. Radiographic control is difficult to assess especially in separating necrosis from tumor progression. There was no attempt to stratify patients treated with Gamma Knife and Linac. Two thirds of the Gamma Knife patients were brain tumors compared to one third of the Linac patients. The Gamma Knife was done at Mayo Clinac and the University of Pittsburgh with better established neurooncology programs and better quality control than the eight Linac sites. In the accompanying editorial Buatti et al discuss some of the issues around the treatment unit issue.</p>

Select Review in Neuro-Oncology

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

Volume: 2, Issue: 1

Title: Glioma Resection Using Intraoperative MRI after Optimal Image-Guided Frameless Stereotactic Resection

Review Type: Meeting Abstract

Category: Adult Neurosurgery

Meeting: Fourth Biennial Satellite Symposium of the AANS/CNS Section on Tumors, April 13-14, 2000

Summary: The aim of this study was to determine the contribution of intraoperative MRI to tumor resection after initial image-guided resection. Studying 39 patients with gliomas, these investigators reported that the use of intraoperative low-field strength open MRI after image-guided frameless stereotactic resection improved the rate of complete resection from 36% to 74%. Following routine frameless stereotactic resection, patients were moved to an adjoining low-field strength open MRI unit for imaging. Fourteen patients (36%) were found to have gross total resection (GTR) after frameless stereotactic resection. In the remaining 25 patients, residual tumor was found. Five patients had tumors in eloquent regions and further resection was not undertaken. However, 20 patients underwent further resection either just outside the MRI gantry or in the adjoining conventional operating room. Sixteen of these 20 patients eventually had GTR with this intraoperative MRI guidance. No complications were experienced using this approach.

Select Review in Neuro-Oncology

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

Volume: 2, Issue: 1

Title: Expression of EGFRvIII is a Better Prognostic Marker for GBM than Either EGFR Expression or Ki-67 Labelling Index

Review Type: Meeting Abstract

Category: Adult Neurosurgery

Meeting: Fourth Biennial Satellite Symposium of the AANS/CNS Section on Tumors, April 13-14, 2000

Summary: These investigators evaluated the effect of EGFRvIII receptor expression on patient survival in a cohort of 47 GBM cases. This receptor is the constitutively-activated and phosphorylated, truncated form of the epidermal growth factor receptor (EGFR). Their hypothesis was that tumors bearing this mutant receptor would have a growth advantage, and that patients whose tumors expressed this receptor would, therefore, have a shorter survival time. A Kaplan-Meier survival analysis revealed that patients with EGFRvIII-positive tumors had a mean survival of 336+/-38 days, compared to 626+/-132 days for EGFRvIII-negative cases ($p=0.16$). They went on to analyze a series of clinical and molecular prognostic factors in a multivariate analysis. Not surprisingly, extent of resection and Karnofsky Performance Status were the most significant prognostic factors. EGFRvIII expression was the most significant molecular marker ($p=0.0838$). Wild-type EGF receptor expression and Ki-67 labelling index were not prognostically significant. The authors suggest that EGFRvIII expression is a more predictive molecular marker of poor prognosis in GBM patients than either wild-type EGFR or Ki-67 expression. This finding is significant insofar as it furthers our understanding of the molecular factors associated with clinical outcome in glioblastoma patients. Other groups are actively pursuing novel treatment strategies aimed at this mutant receptor as a tumor-specific target.

Select Review in Neuro-Oncology

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

Volume: 2, Issue: 1

Title: Patterns of Recurrent Tumor and Radiation Necrosis in 211 Astatine-Labeled Monoclonal Antibody Therapy

Review Type: Meeting Abstract

Category: Neuro-Radiology

Meeting: American Society of Neuroradiology, April 3-8, 2000

Summary: Purpose: To describe patterns of tumor recurrence and radiation necrosis in patients treated with monoclonal antibody (Mab)-labeled with 211 Astatine (At), an alpha particle emitter which delivers a high radiation dose within the margins of the surgically created resection cavity.

Materials & Methods: Eight patients treated with 211 At-labeled 81C6 Mab therapy into a surgically created cavity via infusion catheter underwent serial contrast-enhanced MR imaging at 6-week intervals, with all patients developing new regions of abnormal contrast enhancement. In six subjects a definitive diagnosis of the enhancing region was made by biopsy and in two subjects a presumptive diagnosis was made based on clinical course. MR studies were reviewed for patterns of new contrast enhancement by two neuroradiologists who were aware of biopsy findings.

Results: Four patients had tumor progression (biopsy-proved in 3) and 4 patients had radiation necrosis (biopsy-proved in 3). All 4 patients with radiation necrosis had a pattern of enhancement that was circumferential and symmetric around the surgically created resection cavity and around the catheter tip. All 4 patients with progressive tumor had asymmetric enhancement around the surgical cavity (n=2) or at distant locations (n=2).

Conclusion: Radiation necrosis due to 211 At-labeled 81C6 Mab therapy appears distinguishable from tumor progression on the basis of contrast-enhancement patterns.

Select Review in Neuro-Oncology

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

Volume: 2, Issue: 1

Title: Improved Diagnosis of Brain Tumor Recurrence Using MR Spectroscopy- A Case Study of Patients in the Marimastat Clinical Trial

Review Type: Meeting Abstract

Category: Neuro-Radiology

Meeting: American Society of Neuroradiology, April 3-8, 2000

Summary: Purpose: This study examined the possibility of using 1H MR spectroscopic imaging in addition to MR imaging to improve diagnosis of malignant glioma recurrence following Gamma knife radiosurgery and marimastat chemotherapy.

Materials & Methods: Thirty-one combined MR imaging/MR spectroscopy examinations were performed on eight patients with recurrent gliomas before and after Gamma knife radiosurgery. Patients received 10 mg of marimastat twice daily from the time of Gamma knife until disease progression. MR examinations included pre and postcontrast imaging followed by a 3D 1H-MR spectroscopy acquisition. A neuroradiologist evaluated patient response based on contrast-enhanced T1-weighted MR imaging. These findings were then compared to spectroscopic results.

Results: Three patients showed increases in contrast-enhancing volume of greater than 20 cc within 6 months of radiosurgery. Two of these patients had MR spectroscopy results consistent with recurrence, with increased choline and reduced NAA in regions of new contrast enhancement. The third patient showed large reductions in choline in areas of new enhancement, suggestive of the development of radiation necrosis. This patient had the second longest survival time. Five patients showed moderate increases in contrast-enhancing volume within 1 year of radiosurgery. Two lesions were read as stable, which was consistent with both the MR spectroscopy and the patients' survival times. Analysis of MR imaging data from the remaining three cases attributed the increased contrast enhancement to an indeterminate combination of tumor progression and treatment effect. Analysis of the MR spectroscopy results showed the development of tumor-suggestive patterns in one case and a response to treatment in the other two.

Conclusion: Spectroscopic response and clinical outcome showed similar patterns for this patient sample. MR spectroscopy was particularly useful in patient evaluation for the situations where treatment effects led to ambiguity in the interpretation of conventional contrast-enhanced MR imaging.

Select Review in Neuro-Oncology

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

What's Hot in Neuro-Oncology

Volume: 2, Issue: 1

Title: Immunotoxins and Cytotoxins for Brain Tumor Therapy

Category: Basic Science

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Summary: Standard therapy including surgery, radiation therapy and chemotherapy does not offer clear-cut survival advantage for patients with malignant brain tumors. Therefore, other treatment modalities are necessary. Recent research efforts have focussed on the innovative approaches in which antigens or receptors present on tumor cells can be targeted with specific therapeutic agents (1). These targeted agents may be comprised of an antibody, specific for a membrane antigen (immunotoxin), or a ligand, specific for cell surface receptors (cytotoxin), and toxins derived from bacteria or plants. These targeted toxins can kill tumor cells in a specific manner. Several growth factor receptors have been identified on brain tumors that potentially may serve as a target for tumor targeted cancer therapy. Among these, receptors for epidermal growth factor (EGFR) and transferrin (TfR) have been targeted in vitro and in vivo. EGFR targeted agent, DAB(389)-EGF fusion cytotoxin (made of diphtheria toxin and human EGF) and an immunotoxin composed of an anti-EGFR monoclonal antibody covalently linked to the type 1 ribosomal-inactivating protein have shown tumor cell growth inhibitory activity in vitro and in vivo (see references in 2). Another EGFR targeted cytotoxin, TGF-alpha-PE40 (made of TGF-alpha and mutated form of Pseudomonas exotoxin) has also been produced. TfR targeted immunotoxin, 454A12-rRA (a chemically linked conjugate of a monoclonal antibody against TfR and ricin A chain) and cytotoxin, Tf-CRM107 [made of human transferrin and a mutant of diphtheria toxin (CRM107)] have also been developed. The immunotoxin was tested in the clinic for leptomeningeal neoplasia and cytotoxin has been tested for malignant brain tumors. Tf-CRM107 has been found effective in reducing 50% tumor volume in 60% patients with malignant brain tumor (3). Because TfR are also expressed on normal endothelial cells, a significant dose-limiting peritumoral toxicity was observed.

We have identified a new target in the form of interleukin-4 (IL-4) receptor that is over expressed on malignant brain tumors. To target these receptors, a recombinant chimeric cytotoxin composed of circularly permuted IL-4 and a mutated form of Pseudomonas exotoxin (PE) has been produced. This fusion protein (termed IL-4 cytotoxin) was found to be highly and specifically cytotoxic to brain tumor cells in vitro but not to normal immune and non-immune cells that express lower number of these receptors (4). Preclinical efficacy models of human glioma xenograft in immunodeficient mice have demonstrated a remarkable antitumor activity without any evidence of systemic toxicity. Preclinical toxicology experiments performed in mice, rats, and monkeys have demonstrated that high serum, intracerebral, and cerebrospinal fluid levels can be achieved without any detectable central nervous system or other abnormalities. Based on these results, we initiated intratumor administration of IL-4 cytotoxin for the treatment of malignant brain tumors in a phase I clinical trial (5). In our initial trial IL-4 cytotoxin was directly infused slowly in gliomas of nine patients by intraglioma catheter. No apparent systemic or neurological toxicity occurred in any patient. The infusion of IL-4 toxin in nine evaluable patients with three exceptions showed glioma necrosis as evidenced by diminished gadolinium enhancement by magnetic resonance imaging. Intraoperative biopsy in 5 of 7 patients confirmed extensive necrosis. Two patients were not operated; one showed mottled gadolinium enhancement while the other showed extensive necrosis of tumors by MRI and this patient remains disease free 18 months after the procedure. Additional patients are being treated to determine the maximal tolerated concentration and volume of IL-4 cytotoxin.

About 6 years ago, a new cytokine was cloned which was termed IL-13. Because it had similar biological activities to that of IL-4, we also examined the expression of IL-13 receptors on cancer cells. We first identified receptors for IL-13 on human renal cell carcinoma cells and later, expression of IL-13 receptors on malignant glioma cell lines was demonstrated. To target these receptors, a fusion protein composed of IL-13 and a mutated form of PE (the fusion protein termed IL-13-PE38QQR) was produced. IL-13 cytotoxin has been shown to be highly cytotoxic to IL-13R positive glioma cells in vitro and in animal model for human glioma (6). We have also performed preclinical toxicology and pharmacokinetics studies in mice, rats and monkeys. Based on these studies, a Phase I clinical trial for recurrent malignant glioma has just begun. Thus, IL-4 cytotoxin and IL-13 cytotoxin may be two most useful therapeutic agents for the therapy of brain tumors.

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Select Review in Neuro-Oncology

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Featured Article

Volume: 2, Issue: 1

Title: Report on RTOG 90-05: An Important Faux Pas

Category: Adult Neurosurgery

Journal: IJROBP, Vol: 47, No. 2: pages 291, May 2000

Authors: Shaw, et.al.

Summary: In the May issue of IJROBP Shaw et. al. report the final results of RTOG 90-05, an examination of single dose radiosurgical treatment of recurrent, previously irradiated primary brain tumors and brain metastases. The study was designed as a phase one trial of dose escalation for lesions ranging in size from <20mm, 21-30 mm and > 30 mm. These three size categories were submitted to dose escalation beginning at 18 Gy, 15 Gy and 12 Gy respectively. The maximum tolerated doses (MTD) were determined based on any grade 4 or 5 toxicity or multiple permanent grade 3 toxicities using common toxicity criteria. The principal conclusion of the study was that the MTD was 24 Gy for lesions < 20 mm, 18 Gy for lesions 21-30 mm and 15 Gy for lesions > 30 mm. No toxicity was actually achieved in the group with lesions < 20 mm but physicians were unwilling to move a further escalation to 27 Gy.

Despite this important contribution the article has been commonly cited as evidence of efficacy differences with Gamma Knife Units versus Linear Accelerators. It reports that the Gamma Knife had improved local control. Unfortunately, the reality that the trial was designed as a phase one study of toxicity is ignored. Response is interpreted based on radiographic criteria of a mixed population of glial tumors and metastases. Eighty-four percent of 37 analyzable Gamma Knife patients treated at 2 experienced centers (Mayo Clinic and Pittsburgh) of which 2/3 were glial (otherwise not specified) are compared for radiographic local control with 95% percent of 125 patients treated at 8 relatively inexperienced Linac centers of which 2/3 were metastases (not otherwise specified). Lesions were treated at a range of different doses.

It should be noted that no central radiology review was used, 7.5 % of Linac treatments had documented tumor "miss" and targeting was based on CT or MR scans. It is well known that MR is available at experienced centers and less so at inexperienced centers. It is known that metastases frequently flare radiographically 3-12 months after treatment and often involute later. It is known that target definition affects outcome. It is known that anaplastic and low-grade glial neoplasms are more slowly growing and certainly respond differently than metastases to radiosurgery. These obvious deficits highlight the obvious limit and purpose of study design in reporting results. This reality overshadows any potential that dose prescription habits and radiobiology in the units are fundamentally responsible for an observed difference in response. Several studies (not surprisingly) have failed to reproduce this observation.

In summary, RTOG 90-05 is the first successful national radiosurgical trial because it answers a specifically designed radiosurgical question of MTD. The study was not, however, designed to assess tumor response and progression and the analysis comparing treatment techniques is flawed, primarily due to clear biases that are not accounted in the analysis. The analysis of 90-05 in no way contributes any clarity to the issue of treatment unit as a factor in treatment outcome. This study may demonstrate that, as in all other areas of medicine, that experience and expertise make a difference in results.

It is my hope that science will be respected and that the reality of this unfortunate publishing faux pas will be recognized and put behind us so that important persisting questions in radiosurgery can be addressed and answered. Study design works and we should respect this in reporting.

References: Buatti et. al., IJROBP, vol 47, number 2, pages 269-271