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Title: Correlation between Magnetic Resonance Spectroscopy Imaging and Image-guided Biopsies: Semiquantitative and Qualitative Histopathological Analyses of Patients with Untreated Glioma

Review Type: Article

Category: Adult Neurosurgery


Authors: Croteau D, Scarpace L, et al

Summary:

The authors correlate proton magnetic resonance spectroscopy (1H MRSI) with image-guided stereotactic biopsies to determine the accuracy of MR imaging in the evaluation of tumor extent. 247 tissue samples were obtained from 31 patients with low and high-grade gliomas and spectroscopic information was obtained from coordinate matched regions. The authors found that contrast enhancement and areas of hyper-intensity on T2-weighted images did not define extent of solid or infiltrating tumor respectively. Tumor infiltration and burden did have a positive correlation to increasing choline, decreasing N-acetylaspartate (NAA) and increasing lipid/lactate spectra (relative to spectra obtained from contralateral normal parenchyma).

These findings provide important information about the ability of MR to accurately define tumor extent – information that is increasingly critical as we more tightly focus our surgical, radiotherapeutic and even chemotherapeutic interventions.
Volume 3, Issue 1

**Title:** A multivariate analysis of 416 patients with glioblastoma multiforme: Prognosis, extent of resection, and survival.

**Review Type:** Article

**Category:** Adult Neurosurgery

**Journal:** Journal of Neurosurgery, Vol: 95, No. 2: pages 190-198, August, 2001

**Authors:** Lacroix M, Dima A-S, Fourney DR, Gokaslan ZL, Shi W, DeMonte F, Lang FF, McCutcheon IE, Hassenbusch SJ, Holland E, Hess K, Michael C, Miller D, Sawaya R

**Summary:**

This group of investigators from the University of Texas M.D. Anderson Cancer Center has utilized its large database to identify significant independent predictors of survival in patients with glioblastoma multiforme (GBM), and to determine whether the extent of resection was associated with increased survival time. They retrospectively analyzed 416 patients with histologically-proven GBM (by Ringertz, WHO, and St. Anne-Mayo criteria) who underwent tumor resection at M.D. Anderson between June 1993 and June 1999.

Volumetric tumor assessments had been performed using the Medvision 1.41 computer software program on all cases. This and other tumor characteristics identified on MR imaging were collected prospectively. They also utilized several simple grading scales to identify the proximity of tumor to functional cortex, to characterize preoperative MR features such as mass effect, edema, and enhancement, and to score clinical outcome based on tumor necrosis, patient age, and Karnofsky Performance Scale (KPS) score.

Five independent predictors of survival were identified based on statistical analysis: age, KPS score, extent of resection, and the degree of necrosis and enhancement on preoperative MR imaging studies. A significant survival advantage was associated with resection of 98% or more of tumor volume (13 months median survival) when compared with resections of less than 98% (8.8 months). Using a simple clinical outcome scale (Table 7) ranging from 0 to 5 based on age, KPS score, and radiographic tumor necrosis, Lacroix et al observed significantly longer survival in patients with lower scores (1-3) who underwent aggressive resections, and a trend toward slightly longer survival was found in patients with higher scores (4-5).
Ongoing prospective studies are currently ongoing at this institution to validate further this grading system to determine its usefulness as a prognostic tool.

Nevertheless, the authors concluded that resection of 98% or more of tumor volume, as shown by computer-assisted volumetric studies, is an independent variable associated with longer survival times in patients with GBM, especially when other predictive variables are favorable. In addition to the established clinical prognostic factors of age and preoperative KPS score, the degrees of necrosis and enhancement on preoperative MR studies were significantly associated with survival. This thoughtful retrospective analysis provides a useful framework for conducting a similar prospective study of such patients.

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Volume 3, Issue 1

Title: Large cell/anaplastic medulloblastomas and medullomyoblastomas: clinicopathological and genetic features

Review Type: Article

Category: Adult Neurosurgery


Authors: Leonard JR, Cai DX, Rivet DJ, Kaufman BA, Park TS, Levy BK, Perry A

Summary:

This group of investigators from Washington University in St. Louis present clinical, immunohistochemical, and genetic data of a small subgroup of medulloblastoma cases to support their hypothesis that the large cell/anaplastic (LC/A) variant may represent a tumoral progression of conventional medulloblastomas or medullomyoblastomas. The LC/A variant was originally coined in 1992 by Giangaspero. More recently, others have associated this subgroup of tumors with a more aggressive clinical behavior, including frequent CSF dissemination at presentation.

Of 80 overall cases of medulloblastoma at their institution, 7 (8.8%) were found to fit the histological and immunohistochemical criteria for LC/A medulloblastoma. Clinically, CSF dissemination was identified in all patients and lymph node metastasis was found in one. In five of these cases, the LC/A tumor was found within the setting of either classic or desmoplasmic medulloblastoma or medullomyoblastoma. Fluorescence in situ hybridization (FISH) technology was utilized in 6 cases to assess several genetic features, including the presence of isochromosome 17q (previously found to be characteristic of LC/A tumors), deletion of chromosome 22q (typical of the atypical teratoid/rhabdoid tumor variant of medulloblastoma), and c-myc amplification. Isochromosome 17q was found in 5 of 6 (83%) cases analyzed for this. Amplification of c-myc was found in 3 of 6 cases. In contrast, no 22q deletions were identified.

Leonard et al conclude that the majority of LC/A medulloblastomas arise within a background of typical medulloblastoma or medullomyoblastoma. As in other conventional medulloblastomas, the presence of isochromosome 17q is a common early tumorigenic event; however in a significant percentage of specimens, there is also evidence of aneuploidy and/or amplification of c-myc.
They conclude that the clinical, pathological, and genetic data indicate that LC/A medulloblastomas may arise from anaplastic progression in typical medulloblastomas. They suggest that further study in which multiple samples obtained at different time points during the same patient’s course of disease are investigated may be useful to prove this hypothesis. With the advancement in molecular and genetic techniques for analyzing tumor specimens, it has become increasingly apparent that newly identified tumor subgroups may be clinically relevant with respect to prognosis and response to treatment. Like the atypical teratoid/rhabdoid variant of medulloblastoma, the LC/A variant and its features should be of interest to all neurosurgeons treating such patients.
Volume 3, Issue 1

**Title:** Identification of novel regions of allelic loss in ependymomas by high-resolution allelotyping with 384 microsatellite markers.

**Review Type:** Article

**Category:** Adult Neurosurgery


**Authors:** Tong, CYK, Zheung PP, et al.

**Summary:**

Ependymomas are uncommon tumors in adults, occurring predominantly in children. Previous studies have indicated that structural abnormalities of chromosomes 6, 11, 17 and 22 are not uncommon. The most common abnormalities within this group was monosomy of chromosomes 17 and 22, indicating that at least 2 tumor suppressor genes (TSGs) may be responsible for the tumorigenesis in ependymomas. The current authors have published previously on their results of CGH to detect genetic abnormalities in ependymomas, and extend this investigation with the use of 384 microsatellite markers in 16 tumors over 39 nonacrocentric chromosome arms.

In the present study a 50% level of loss of heterozygosity (LOH) was considered significant. The authors found high rates of LOH in chromosomes 13q, 16p, 16q, 19q, 20p, and 20q. Using their high-resolution allelotyping, the authors were able to narrow down the area on each arm of a chromosome showing an overlapping small deletion region (OSDR). Allelic gains and losses were confirmed with CGH. While the authors confirmed their prior findings of LOH in chromosomes 6, 17 and 22, they also identified new sites of interest on chromosomes 13, 16, 19 and 20. This work provides leads for the identification of possible new TSGs involved in the development of ependymomas.
Volume 3, Issue 1

Title: Predictive value of progression-associated chromosomal aberrations for the prognosis of meningiomas: a retrospective study of 198 cases.

Review Type: Article

Category: Adult Neurosurgery


Authors: Ketter R, Henn W, et al.

Summary:

Between 1992 and 1998, 198 patients with Simpson Grade 1 or 2 resection were followed for a mean period of 33 months. The goal was to determine whether cytogenetic changes were suitable as a predictive factor in prognosis. On the basis of standard cytogenetics the tumors were divided into 4 groups: Group 0 had a normal diploid set; Group 1 had monosomy of 22 alone; Group 2 tumors had monosomy of 22 plus a hypodiploid set of autosomes; Group 3 had loss of 1p plus other aberrations including monosomy 22. Recurrence rates were 4.3% in Groups 0 and 1; 10.5% in Group 2; and 30% in Group 3. Histologic grade and location were also important in predicting recurrence. In 27.3% of cases monosomy 22 was the sole abnormality while deletion of 1p was seen in 20.2%.

Spinal meningiomas belonged exclusively to Groups 0 and 1, not associated with progression. Convexity associated tumors were much more likely to be from Groups 2 or 3 than skull base tumors (p<0.0001). In the proposed algorhythm for management, patients at risk for recurrence include histologic WHO grade II or III tumors and/or Group 2 or 3 cytogenetic changes and WHO I tumors with Group 2 or 3 changes. Given the labor intensive nature of cytogenetics, I look forward to the same group coming forward with a similar analysis utilizing a more efficient method of chromosomal or genetic analysis.

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Volume 3, Issue 1

Title: Low Grade Hemispheric Gliomas in Adults: a critical review of extent of resection as a factor influencing outcome

Review Type: Article

Category: Adult Neurosurgery


Authors: Keles GE, Lamborn KR, Berger MS

Summary:

This article is preceded by an editorial on the topic by Dr. Ed Laws, pp.731-732, and a response by the authors. The authors reviewed the English language literature on surgery for low grade gliomas from 1970 to 2000. Thirty studies were identified. Of these only 5 had > 75 patients without children and/or pilocytic or gemistocytic subtypes.

Table 1 includes all 30 studies in which there was statistical analysis of prognostic effect of extent of resection on survival. None of these studies were prospective randomized studies. There was an increase in the number of publications supporting more extensive resections as well as those that did not. Table 2 listed 16 studies in which the prognostic effect of GTR was assessed. In 10 of these studies that provided 5 year survival estimates the survival rate was higher in those who underwent GTR (51-100% 5 yr. survivals) compared to those who lesser extent of resection. Table 3 listed those studies were the prognostic effect of extent of resection on survival with GTR not evaluated as a distinct group. Of the 9 studies with 5 year survival estimates, only 2 showed a benefit for greater extent of resection on multivariate analysis. Of the 4 studies without 5 year survival estimates only 1 showed a benefit. Table 4 reviewed the 5 series that met the authors most strict analysis standards (above). Of these only 4 showed a benefit for extent of resection on improving survival.

In their conclusions the authors correctly state that this review of the available Class II data has many limitations. However it is unlikely that randomized studies of surgery will ever be performed. Until then the advantages of more aggressive resection must be gleamed from the small, but increasing, number of studies that show a survival benefit.
Volume 3, Issue 1

Title: Combination of stereotactic radiosurgery and cytokine gene-transduced tumor cell vaccination: a new strategy against metastatic brain tumors

Review Type: Article

Category: Adult Neurosurgery


Authors: Nakahara N, Okada H, et al.

Summary:

Brain metastases are the most common brain tumor in adults. Standard therapies with surgery, external radiation, radiosurgery and brachytherapy produce very good local control rates. Relapse elsewhere in brain or at the primary site is common in long term survivors. The authors evaluated a novel combination of radiosurgery and an IL-4 or GM-CSF transfected tumor cell vaccine in a rat model of brain metastases. The rat mammary adenocarcinoma cell line MADB106 was transfected with either GM-CSF or IL-4 and the stable expression of the gene products were confirmed and the cell lines expanded.

55 rats were used for the study: 34 animals were assigned to the vaccination group with MADB106-GM-CSF or MADB106-IL-4 injected into the flank on day 3 after intracranial implantation of MADB106 tumor cells. 27 animals were assigned to irradiation receiving 32 Gy on Day 5 after brain tumor implantation. There were 6 treatment groups: 1) brain implant alone, no treatment (n=11); 2) MADB106-GM-CSF vaccine alone (n=11); 3) MADB106-IL-4 vaccine alone (n=6); 4) radiosurgery alone (n=10); 5) combined MADB106-GM-CSF vaccine and radiosurgery (n=11); 6) combined MADB106-IL-4 vaccine and radiosurgery (n=6). Long term survivors were re-challenged with another tumor implant at day 55 in the opposite hemisphere. Results: No animals from the untreated group survived more than 21 days. Radiosurgery alone animals survived longer than untreated rats (P<0.0001) but only 1/10 survived longer than 55 days. In the radiosurgery plus vaccine groups 14/17 rats lived longer than 55 days (P<0.0003). In the re-challenged rats all those that received combination therapy survived longer than 50 days.

Histologic findings of tumors showed prominent infiltration of tumor by...
CD11b/c cells in treated animals (radiosurgery alone or with vaccine). CD4 cells were present infiltrating the tumors of combined and vaccine alone groups. The authors provided some theories as to why combination therapy worked best and why radiosurgery had a role to play in that process. This work provides some impetus for further studies and possible clinical trials using combination therapy for primary and recurrent brain metastases.
Volume 3, Issue 1

**Title:** Inhibition of Glioma Angiogenesis and Growth In Vivo by Systemic Treatment with a Monoclonal Antibody Against Vascular Endothelial Growth Factor Receptor-2

**Review Type:** Article

**Category:** Basic Science


**Authors:** Kunkel P, Ulbricht U, Bohlen P, Brockmann MA, Fillbrandt R, Stavrou D, Westphal M, Lamszus K.

**Summary:**

In this study, the authors used an orthotopic intracerebral model to determine whether systemic treatment with the monoclonal antibody DC101 against vascular endothelial growth factor receptor-2 could inhibit angiogenesis and growth of the glioblastoma cell line G55. Two treatments regimens were compared. In one, the antibody, control IgG, or PBS were administered on the day of tumor implantation for 16 days. In the second, treatment was initiated on day 6 after treatment. The tumors were assessed for tumor volume, morphology, microvessel density, cell proliferation, and apoptosis.

Their results indicated that blockade of the VEGFR-2 by systemic treatment of DC101 inhibits angiogenesis and tumor growth. Tumor volumes were decreased by 59% and by 81% in comparison with IgG and PBS controls, respectively, when treatment was administered immediately. Similar results were obtained with the delayed treatment. Microvessel density was decreased by 40%. As well, they observed a decrease in tumor cell proliferation and an increase in apoptosis.

Morphological analysis revealed a significant increase in the number of and total area of satellite tumors clustered around the main tumor mass. These satellites usually contained central vessel cores and the tumor cells had migrated long distances along theses vessels. The authors interpret their data to suggest that in a therapeutic situation where angiogenesis is inhibited, the blockade of neovascularization favors host vessel cooption. Therefore, while the treatment inhibited angiogenesis and decreased tumor volume, at the same time, it caused an increase in tumor invasiveness along host microvasculature.
These findings demonstrate the necessity to evaluate antiangiogenic therapies in orthotopic models for adverse outcomes not originally anticipated. The authors further suggest that a combination of different treatment regimens, which also include anti-invasive therapy, may be needed for an effective therapy against glioblastoma, and the use of this antibody may be one effective component.
Volume 3, Issue 1

Title: Detection of JC Virus DNA Sequences and Expression of the Viral Regulatory Protein T-Antigen in Tumors of the Central Nervous System

Review Type: Article

Category: Basic Science


Summary:

The JC virus (JCV) is a neurotropic polyomavirus that possesses an oncogenic potential to induce the development of various neuroectodermal tumors including medulloblastoma and glioblastoma in experimental animals. The oncogenicity is attributed to the viral early T-antigen gene product, which has the ability to associate with and suppress the p53 and Rb tumor suppressor proteins. Since the JCV infects greater than 70% of the human population during early childhood, the authors of this study examined 85 clinical specimens for evidence of JCV sequence and T-antigen expression. Specimens included oligodendrogliomas, fibrillary astrocytomas, pilocytic astrocytomas, mixed oligoastrocytomas, anaplastic astrocytomas, glioblastomas, ependymomas, a gliosarcoma, a gliomatosis cerebri, and a sub-ependymoma.

PCR analysis indicated that viral early sequence as detected in 69% of the specimens and T-antigen was detected immunohistochemically in the nuclei of 32.9% of the specimens. Virus sequence was detected in every type of tumor, and with the exception of anaplastic astrocytoma, T-antigen was also expressed in all types of tumors. These observations demonstrating the detection of JCV sequence and T-antigen expression in various human brain tumors in conjunction with earlier observations that indicated that 1) JCV is mutagenic and has the ability to transform cells in culture, 2) JCV induces a variety of CNS tumors in animal models, 3) the tumors induced in animals closely resemble those seen in pediatric patients, 4) reactivation of JCV in PML brain induces giant bizarre astrocytes with pleomorphic hyperchromatic nuclei resembling malignant astrocytes of pleomorphic glioblastomas, and 5) JCV is widespread in the human population, suggest that this ubiquitous human virus may be associated with the development of some, if not all, of the various types of brain tumors.
Volume 3, Issue 1

Title: Simultaneous Inhibition of Glioma Angiogenesis, Cell Proliferation, and Invasion by a Naturally Occurring Fragment of Human Metalloproteinase-2

Review Type: Article

Category: Basic Science


Summary:

In this study, the authors demonstrated that glioma cells in culture secrete an autocatalytically derived MMP-2 fragment called PEX. The purified protein was found alone or in complex with TIMP-2. Analysis of PEX expression in human gliomas indicated that its expression correlated with tumor grade and histological subtype, being highly expressed in the more aggressive, vascularized, and proliferative astrocytic tumors. Using a tube formation assay, PEX was found to inhibit tube formation of HUVEC, BCE and PAE cells transfected with KDR. Using the Boyden chamber and monolayer migration assays, PEX was found to decrease migration of both endothelial and U87MG, U373MG, and U118MG glioma cells. In addition, it inhibited glioma and endothelial cell proliferation and this inhibitory activity was accompanied by increased apoptosis. Using in vivo studies, systemically administered PEX was found to inhibit glioma growth of U87MG s.c. xenografts and intracranial implants by 99%. Growth inhibition was characterized by decreased vessel count, decreased proliferative index, and increased apoptotic index. There were no detectable signs of local or systemic toxicity.

The authors suggest that the antitumor activity of PEX is not in contradiction with the finding of increased expression with increased tumor grade. Rather, they argue that proangiogenic factors override PEX. Further, they suggest that treatment with purified human PEX protein would, in turn, override the proangiogenic factors resulting in potent inhibition of malignant tumor growth by both angiogenesis-dependent and -independent mechanisms. Therefore, the authors conclude that PEX is a powerful candidate for the treatment of malignant tumors.
Volume 3, Issue 1

Title: Monoclonal Antibody 806 Inhibits the Growth of Tumor Xenografts Expressing Either the de2-7 or Amplified Epidermal Growth Factor Receptor (EGFR) but not Wild-Type EGFR

Review Type: Article

Category: Basic Science


Authors: Luwor RB, Johns TG, Murone C, Huang H-JS, Cavenee WK, Ritter G, Old LJ, Burgess AW, Scott AM

Summary:

The monoclonal antibody 806 was raised against the delta2-7 epidermal growth factor receptor, a truncated version of the EGFR commonly expressed on gliomas. The antibody not only bound to the deleted receptor but also to the wild-type receptor in cells exhibiting amplification of the EGFR gene. It did not bind to cells or normal tissue expressing the wild-type receptor in the absence of gene amplification. This specificity offers advantages over current EGFR antibodies that are toxic to liver and skin in humans.

To assess the antitumor activity of this monoclonal, tumor cells were inoculated subcutaneously, and two regimens of antibody treatment were explored. A preventive regimen consisted of treatment starting the day before tumor cell inoculation; while an established regimen consisted of treatment when a mean tumor volume of 65 mm3 for U87MGdelta 2-7, 84 mm3 for U87MG, and 73 mm3 for U87MG.wtEGFR (mimics cells with gene amplification).

For the preventive model, the antibody had no effect on tumor growth of parental U87 xenografts expressing wild-type EGFR, but significantly inhibited the growth of U87MG delta2-7 in a dose-dependent manner. For the established model, the antibody again had no effect on the parental cells, but also significantly inhibited the deltaEGFR2-7 xenografts in a dose-dependent manner. To determine whether the antibody was also effective against tumor cells expressing high levels of wild-type receptor, tumors expressing U87MG.wtEGFR were also treated. The antibody significantly inhibited the growth of these tumors as well.

Histological assessment of the tumors revealed large areas of necrosis,
supporting the hypothesis that the monoclonal antibody 806 induced decreased cell viability. The authors conclude that the unique specificity of this antibody suggests immunotherapeutic potential in targeting a number of tumors types, particularly head and neck tumors and gliomas, without the restrictions associated with normal tissue uptake.

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Volume 3, Issue 1

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

Review Type: Article

Category: Medical Oncology


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

Summary:

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

The authors studied frozen tissue specimens from 47 consecutive patients with malignant glioma. The MGMT promoter in tumor DNA was analyzed with a methylation-specific PCR assay and these results were correlated with clinical parameters. Nineteen of 47 patients (40%) demonstrated methylation of the MGMT promoter; methylated and unmethylated samples, although small in total number, were equitably distributed with respect to age, KPS, and histology (astrocytoma WHO grade III [n=18] vs. grade IV [n=29]).

Clinically, all patients were treated with intra-arterial cisplatin, ‘whole brain’ radiotherapy, and a median of three courses of IV BCNU. Twelve of 19 patients with methylated tumors (63%) had a partial (PR) or complete response (CR) to BCNU, as compared to only one of 28 patients with unmethylated tumors (4%) showing radiographic response. The median time to radiographic progression was 21 months in the former group and only 8 months in the latter. The authors conclude that methylation status of the MGMT promoter is an independent and stronger predictor than any other known clinical / pathological parameter used in practice today.

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

Although a prospective pharmacogenomic study comparing patients who receive monotherapy with IV BCNU to those placed in a placebo group would likely be revealing, this study design poses an ethical dilemma. Perhaps a larger, more homogenous group can be studied in the future (e.g. all patients with glioblastoma), with all patients being followed for survival as an important secondary endpoint. Because state-of-the-art care for patients with glioblastoma multiforme most often calls for multiple, individualized drug regimens, one can concede that the MGMT issue may be difficult to fully elucidate. Nevertheless, the data presented in this article are compelling and reveal credible evidence of a correlation between survival after BCNU therapy and MGMT methylation.
Volume 3, Issue 1

Title: Randomized Trial of Procarbazine, Lomustine, and Vincristine in the Adjuvant Treatment of High-Grade Astrocytoma: A Medical Research Council Trial.

Review Type: Article

Category: Medical Oncology


Authors: Medical Research Council Brain Tumour Working Party.

Summary:

The Medical Research Council Brain Tumour Working Party conducted a large-scale randomized trial to evaluate the efficacy of PCV (procarbazine, CCNU, vincristine) chemotherapy for adults with newly diagnosed malignant glioma. Over a 10-year period, 674 patients (pts) were randomized to either RT (involved field radiation therapy) (n=339) or RT + PCV (n=335). RT dosage, fields, and fractions (fx) were initially restricted to one of two schedules: 45 Gray (Gy) in 20 fx (n=135) vs. 60 Gy in 30 fx (n=501) with parallel opposed or three field technique. Later in the study, other radiation schedules were permitted (n=38). PCV dosing scheme was "non-traditional" with procarbazine being given at 100 mg/m2 days 1-10, CCNU 100 mg/m2 on day 1, and vincristine at 1.5 mg/m2 with a 2 mg max on day 1 of a 42-day cycle.

The primary endpoint was survival from date of randomization and the secondary endpoint was progression-free survival. No radiographic endpoint was utilized. No formal quality of life instruments were administered. The trial was designed to detect a 10% increase in survival at 2 years with 90% power at 5% (2-sided) significance. Of note, 19% of 335 pts allocated PCV did not start chemotherapy (principally due to pt deterioration or withdrawal of consent). Those who did get PCV received a median dosage of 3 cycles. Use of chemotherapy on progression was relatively infrequent (RT 20%, RT-PCV 10%). The authors reported that the PCV schedule improved survival by 1.7% and median survival by approximately 2 weeks. This was not deemed significant based on the initial hypothesis put forth. As such, the authors suggest that a chemotherapy "no treatment arm" is ethical for treatment of malignant glioma.

Several issues were outlined in a subsequent letter to the editor (JCO, Vol
19, No 19 [Oct 1], 2001: pp 3997-4001. 1) There was no statistical correlation of survival with the accepted prognostic variables of age, performance status, histologic grade, and extent of resection. 2) The median survival of the anaplastic astrocytoma (AA) subgroup (20% of the study population) in this study was 13 months as opposed to an expected 45 months. 3) Eligibility parameters were vague. 4) Twice as many patients randomized initially to the radiotherapy-only arm received subsequent chemotherapy at recurrence, which may have influenced ultimate survival differences between the two treatment arms.

The authors replied that: 1) The stated prognostic variables are indeed significant in terms of survival, but not predictive of chemotherapy response. 2) The median AA survival time point does not accurately reflect the overall survival curve; this can be seen in the differences between AA and GBM groups in this trial. Also, differences in surgical practice parameters from center to center may have biased pt outcome. 3) Entry criteria were broad to reflect practice outside the trial setting. Randomization should have equalized the parameters in question. 4) The impact of re-treatment was probably low given that the "most effective" regimen is the one in question.

This study should serve as a wake-up call to oncologists who have become complacent with the administration of PCV for primary treatment of pts with malignant glioma. This practice is based on experience from smaller cohorts that frequently included chemosensitive oligo-containing tumors. Similarly, treatment with single agent IV BCNU has frequently been justified by reference to marginal RTOG data from 3 decades past. Over time, single agent IV BCNU appears to have grandfathered into an FDA-approved and expected norm.

Eligibility for enrollment in Phase I and II clinical trials must be reviewed preferentially in order to hasten the pathway to a cure for malignant glioma. Treating institutions should set enrollment goals of 10-20% for this patient population. Promising, less toxic, therapies such as temozolomide, irinotecan, tamoxifen, thalidomide, retinoic acid, and others may be considered in lieu of traditional nitrosoureas when appropriate. Finally, multimodality treatment utilizing surgery, radiation, chemotherapy and biological therapies in an aggressive yet prudent fashion will undoubtedly improve overall patient outcome until a cure is found.

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Volume 3, Issue 1

Title: Brain Tumors

Review Type: Article

Category: Medical Oncology


Authors: DeAngelis, LM.

Summary:

This review article focuses on the general presentation, diagnosis, and treatment of glial tumors (astrocytomas, oligodendrogliomas), meningiomas, and primary central nervous system lymphoma (PCNSL). The summary below will review astrocytomas and meningiomas as these conditions constitute the bulk of the article.

The author begins by condensing the epidemiology of intracranial neoplasms based on American Cancer Society data from 1999. There were 16,800 new intracranial tumor diagnoses and primary CNS cancer was the cause of death in approximately 13,100 people that year. According to a Mayo series and subsequent CBTRUS data, the age and sex adjusted incidence of primary tumors of the CNS is about 11.5 per 100,000 persons. More than 100,000 patients per year die with symptomatic intracranial metastases. Not reviewed in the article is the disproportionately heavy disability inflicted by brain tumors when compared to other cancers.

Astrocytomas are separated into World Health Organization (WHO) grade I (e.g. pilocytic astrocytoma), WHO grade II (e.g. low-grade fibrillary astrocytoma), WHO grade III (anaplastic astrocytoma [AA]), and WHO grade IV (glioblastoma multiforme [GBM]). With respect to low-grade fibrillary astrocytomas, the peak incidence is in the third to fourth decade of life, the first clinical manifestation is many times a seizure, and brain MRI reveals a diffuse, nonenhancing mass that is hypointense on T1 and best seen on T2 or FLAIR sequences. Positron Emission Tomography (PET) may be useful for discriminating biologically more aggressive areas of tumor and for treatment planning. Maximum feasible resection is advisable. Lower doses of involved field radiation treatment (IFRT) (approximately 50.4 Gray [Gy]) are better tolerated and as effective as higher doses (approximately 60 Gy). There does not appear to be a survival benefit with respect to the timing of radiation treatment (treatment at discovery vs. treatment of clinical or...
radiographic progression). Median survival is five years although the range of survival is wide and unpredictable.

Malignant gliomas (AA and GBM) are the most common glial neoplasms with 80% of these being GBM. Primary GBMs (de novo) tend to occur in older patients (mean age, 55 years) and secondary GBMs (arising from lower grade astrocytoma) tend to occur in younger adults (mean age, 45 years). The MRI in GBM typically shows a heterogeneously contrast enhancing lesion surrounded by vasogenic edema and non-contrast enhancing tumor. The treatment approach for GBM and AA is similar. Maximum feasible resection is advisable as gross total resection is associated with better outcome. Surgery is followed by IFRT to 60 Gy and there may be additional benefit to stereotactic radiosurgical boost when indicated. To date, the benefit from chemotherapy has been limited, although there may an increase in the proportion of long-term survivors with use of an agent such as BCNU. Despite aggressive treatment, most patients die of the disease with median survival of about 3 years for AA and one year for GBM.

Meningiomas constitute approximately 20 percent of intracranial neoplasms but the majority are asymptomatic. The incidence in symptomatic patients is about 2 per 100,000. Meningiomas occur more frequently in women with a female to male ratio of 3:2 or even 2:1 in some series. All meningiomas are characterized by the loss of chromosome 22q, which is also the molecular characteristic of neurofibromatosis 2. Meningiomas occur primarily at the skull base, in the parasellar regions, and over the cerebral convexities. On MRI, meningiomas usually have a ‘dural tail’ and a characteristic diffuse pattern of enhancement. Small meningiomas may simply be followed, particularly in older patients. Surgery is definitive therapy if possible. Stereotactic radiosurgery is another treatment option for tumors less than 3 cm diameter. Chemotherapy has been disappointingly limited in impact for this condition.

This review was thoughtful and concise. The remainder of it discussed the importance of discriminating oligodendrogliomas from astrocytomas and treatment differences in these regards. PCNSL and oligodendroglioma have been two limited success stories of neuro-oncology. Perhaps this is not because of the discovery of particularly innovative or specific treatment strategies, but rather because of the identification and discrimination of these disease states from other primary brain tumors that are less amenable to therapy. Because of the focus of this article, new treatment strategies for the conditions listed were not reviewed.
**Volume 3, Issue 1**

**Title:** A Phase III Study of Radiation Therapy Plus Carmustine with or without Recombinant Interferon-alpha in the Treatment of Patients with Newly Diagnosed High-Grade Glioma.

**Review Type:** Article

**Category:** Medical Oncology


**Authors:** Buckner, JC, Shomberg, PJ, McGinnis, WL, et al.

**Summary:**

Three hundred eighty three patients meeting eligibility criteria were registered to begin concurrent involved field radiation therapy (IFRT) and IV BCNU for treatment of newly diagnosed malignant glioma. The planned total dose of brain irradiation was 50.4 Gray (Gy) to the involved field with a 14.4 Gy boost to the contrast enhancing tumor bed + 2 cm margin. The BCNU dose was 200 mg/m2 within 3 days of the initiation of radiation therapy (no interferon during IFRT). After the completion of radiation, patients were stratified by age, extent of surgery, tumor grade, histology, ECOG status, and treating institution. The patients were subsequently randomized to ARM A) BCNU alone at 200 mg/m^2^ every 7 weeks for up to 1 year to a maximum of 6 cycles or until disease progression or ARM B) BCNU at 150 mg/m^2^ every 7 weeks (day 3) for up to 1 year to a maximum of 6 cycles or until disease progression + 12 x 10^6^ U/m2 on days 1-3 of weeks 1, 3, and 5 of each 7-week cycle.

Between April 1990 and June 1994, 383 patients were enrolled in the induction phase of the study. Of these, 20 patients were ineligible and 3 patients dropped out of the study before treatment began. Of the 360 patients who began radiation therapy, 320 completed the therapy: 295 per protocol. In 10 patients, there were insufficient data to assess compliance with protocol. Also, 10 of the 20 ineligible patients noted above were randomized and included in the final analysis. Thus, of 360 eligible patients who began study treatment, a total of 275 (137 Arm A and 138 Arm B) were randomized and assessed.

The study arms were well balanced. The median time to tumor progression (TTP) was 169 days for patients on Arm A and 148 days for patients on Arm B. The median survival after randomization was 357 days for the patients on Arm A and 300 days for patients on Arm B. Subset analysis found no
significant difference between postrandomization TTP or survival between the two treatment arms. There was no difference in response rates between the 2 treatment arms in 214 evaluable patients. Despite the greater acute toxicities associated with IFN-alpha, the number of patients who withdrew from protocol therapy for toxicity or who refused to continue treatment was nearly identical. Of note, higher baseline mini-mental status exam scores were prognostic of better survival and TTP.

Despite preclinical studies suggesting benefit to combining BCNU and IFN-alpha, this well designed study proved that there was no difference in terms of survival or TTP when these potentially noxious drugs were co-administered in the clinical setting. The importance of reporting a negative study is also clear and adherent with excellent scientific practice. As a commentary, given the limited survival benefit of single agent IV BCNU to begin with, one is reminded that the standard administration of IV BCNU is marginal treatment. The neuro-oncology community should continue to look past single agent IV BCNU as a standard and explore new therapies more vigorously and earlier in the course of disease. Innovative clinical trials are the only way to push forward our attempts to eradicate this disease.
Volume 3, Issue 1

Title: Oligodendrogliomas: Reproducibility and Prognostic Value of Histologic Diagnosis and Grading

Review Type: Article

Category: Neuro-Pathology


Authors: Giannini, C, Scheithauer, BW, Weaver, AL, et al

Summary:

Seven neuropathologists and 6 surgical pathologists experienced in brain tumors histologically assessed 124 tumors from Mayo clinic material, originally diagnosed as oligodendrogial neoplasms of any grade between 1960 and 1990. The aim was to evaluate interobserver reproducibility in the identification of histologic features used in classification and grading. Statistically reproducible parameters (features showing >60% consensus) were then evaluated for prognostic significance (cause-specific survival by Cox regression fit).

The authors identified features used in several histologic schemes for grading of oligodendrogliomas. The features were defined for use by participants, who used a form to indicate whether features were present or absent and indicating the degree of certain parameters. High or predominant cellularity, presence and number of mitoses per 10 hpf, microcalcification, endothelial hypertrophy, endothelial proliferation, and necrosis were identified as showing sufficient concordance to justify evaluation for prognostic significance. Univariate analysis revealed high cellularity, presence of mitoses, endothelial hypertrophy, endothelial proliferation and necrosis to be associated with survival. Vascular changes had a particularly high association (p<0.001). While the mitotic index was found associated with survival when individual pathologists were evaluated, there was lack of concordance between pathologists (apparently largely attributed to cases with rare mitoses). There was slightly more agreement among neuropathologists than surgical pathologists on some of these features, particularly vascular parameters.

The study confirms the reproducibility and prognostic importance of some of the features used in current oligodendroglioma grading schemes, particularly endothelial hypertrophy, mitoses, and necrosis. The results point to an
acknowledged problem in reproducibility of mitoses counting in grading, but still found prognostic significance. The study does not address the more complex difficulty which exists in some cases of distinguishing oligodendrogliomas or mixed oligodendrogliomas from other types of gliomas.
Volume 3, Issue 1

Title: Extraventricular Neurocytomas

Review Type: Article

Category: Neuro-Pathology


Authors: Brat, DJ, Scheithauer, BW, Eberhart CG, and Burger, PC.

Summary:

The authors describe the pathologic features, clinical data, and imaging characteristics of 35 gliomas they classified as extraventricular neurocytomas. The group of tumors showed no gender predominance, occurred in patients between 5 and 76 years age (median 34 yrs), and involved the cerebrum. On imaging, these were solitary, variably contrast-enhancing, and 57% were cystic.

Histologic features appeared to resembled those of central neurocytoma, as illustrated. They were described as formed of cells with finely granular slightly eosinophilic or cleared cytoplasm, round oligodendroglial like nuclei forming clusters, sheets, ribbons, or rosettes associated with arrangements of neuropil. A solid pattern with sparse neuropil occurred in 83% of the cases, cell clusters with intervening neuropil was seen in 71%. Strong synaptophysin immunoreactivity was one defining feature.

GFAP immunoreactivity in neurocytic-like cells was reported in 46%, ganglion cell differentiation in 66%. Mitotic rate was low in most (23 showed 1 or less per 10HPF, but 9 had 3 or more per 10HPF with the highest 9 per 10 HPF. The interface with brain parenchyma was usually but not always well defined. Eleven of the tumors were considered “atypical” due to combinations of necrosis, vascular proliferation, and mitotic activity greater than 3 per 10 HPF. Treatment was not uniform, 17 received radiation therapy, 19 were subtotally resected or biopsied only. Follow-up was from 6 to 96 months. In 30 cases with follow-up, 10 recurred with 3 causing death at 6, 14, and 43 months. 10 of 19 recurrences followed subtotal resections with median interval 17 months. None of the 11 “totally resected“ tumors with follow-up recurred.

Other factors which appeared related to recurrence risk included older age (mean age of recurrent tumors was 53 yrs vs 27 yrs). 5 of 10 tumors that
recurred were “atypical” histologically, 4 or 9 that did not recur after subtotal resection were “atypical” histologically. However, all of the deaths occurred in “atypical” histologies with high MIB1 (8.8%). 6 of 10 biopsied or subtotally resected tumors that recurred had been radiated, 6 of 9 subtotally resected tumors that did not recur had been radiated.

The study describes, as others have as well, gliomas with histologies similar to central neurocytomas occurring away from the ventricles. Unfortunately, 8 of 20 cases that had not recurred were followed for a length of time near or less than the median time to recurrence, limiting the meaningfulness of those cases. The study found that the extent of resection achieved was the best factor to predict lack of recurrence. The histologic recognition of these neoplasms and distinction from some forms of ependymoma, oligodendroglioma or other glioneuronal tumors may be difficult or controversial in some cases.
Volume 3, Issue 1

Title: Glioblastomas with an Oligodendroglial Component: A Pathological and Molecular Study

Review Type: Article

Category: Neuro-Pathology


Authors: He J, Mokhtari, K, Sanson, M, et al

Summary:

25 glioblastomas multiformes which were interpreted to show an oligodendrogial component were analyzed for LOH on 1p and 19q (oligodendroglioma-associated abnormalities), and for EGFR amplification, P16 del, LOH 10q, PTEN and TP53 (among markers of progression of astrocytic tumors to GBM). The morphologic features used to identify this set of GBMs included gliomas with a component of poorly differentiated astrocytic cells with features of grade IV Astrocytoma (WHO) which also showed a component of "anaplastic oligodendrogial-like" cells with branching capillary network. GBMs with only scattered oligodendroglial-like cells were excluded. Among the findings were LOH for 1p in 40%, LOH 19q in 60%, with 28% showing both. EGFR amplification was seen in 44%, LOH 10q in 64%, and TP53 mutations in 24%. P16 deletion was seen in 16%,PTEN in 11%. They identified only the incidence of EGFR amplification as a difference between the findings of "primary" and "secondary" groups (11/20 in primary vs 0/5 secondary).

The authors studied a group of GBMs with an oligodendroglioma-like component, a group which comprised 17% of the group of GBMs they reviewed to derive the sample. Most (20) were of the "de novo" type. They report an incidence of oligodendroglioma-associated genetic alterations which exceeds that which has been reported by others in unselected GBMs. This group of GBMs showed a complement of genetic abnormalities frequently seen in unselected GBMs as well. The study did not specifically look at behavior or survival, but the authors report that the age and survival of these patients were similar to those of unselected GBM. Thus, the clinical importance of the morphological appearance of an oligodendroglial component in GBM remains to be further elucidated, but the findings suggest that a molecular-genetic may exist in this group.
Volume 3, Issue 1

Title: Significance of MIB-1 staining indices in meningiomas

Review Type: Article

Category: Neuro-Pathology


Authors: Nakasu, S, Li, DH, Okabe, H, et al.

Summary:

The authors evaluated MIB-1 immunohistochemistry staining indices in 139 meningiomas (including 2 anaplastic and 12 atypical), using then comparing two counting methods. They simply compared MIB-1 indices obtained using areas of highest labeling (HL) to MIB-1 indices obtained by random counts (RC). Not surprisingly indices were higher in HL method, approximately twice that obtained by the random method. The results of the methods showed close correlation, both methods showed significant separation with grade of meningioma (benign, atypical, anaplastic), and provided information in predicting recurrence. When examined with respect to recurrence risk, in the 112 totally resected meningiomas, the random method was a better predictor of recurrence than the HL method. The authors note that they observed otherwise benign meningiomas which did not recur, with focally elevated MIB-1 indices. They suggest that such focal elevation in MIB-1 in meningiomas does not contribute to recurrence, but would result in elevated MIB-1 if HL methods of counting were used.

MIB-1 is frequently used as an adjunct in the histologic evaluation of neoplasms to evaluate proliferative activity. In meningiomas, while proliferative rate appears to be important in predicting recurrence, some conflicting results with respect to prognostic importance of MIB-1 are in the literature. Tumor heterogeneity/geographic variability of staining is noticeable by anyone who performs these studies. In some tumor types, it has been suggested that areas of highest labeling be evaluated. However, in some neoplasms this may not be the best approach. The results in this series of meningiomas simply re-emphasizes interpretive technique and suggests focal elevations in MIB-1 labeling rate may not be of prognostic significance.
Volume 3, Issue 1

Title: Pictorial Essay: Primary Lymphoma of the Central Nervous System: Typical and Atypical CT and MR Imaging Appearances

Review Type: Article

Category: Neuro-Radiology


Authors: Erdag N, Bhorade R, Alberico R, Yousuf N, Patel M

Summary:

The authors review the appearance of primary CNS lymphoma (PCNSL) in immunocompetent and immunocompromised individuals. This pictorial essay includes many excellent MRI and some CT images of a wide range of typical and less common imaging presentations of PCNSL. All imaging is of the intracranial compartment (no spinal imaging presented).

The authors review that PCNSL in immunocompetent patients tends to present as a large cellular (increased attenuation on non-contrast CT; hypo/isointense on T1 and T2-weighted MR) deep hemispheric masses that demonstrate homogeneous enhancement. Such masses often approach or cross the midline and rarely mineralize (pre-therapy) and are rarely hemorrhagic. Note is made that secondary CNS lymphomas tend to be leptomeningeal/dural in location.

PCNSL in immunocompromised (HIV, congenital immune system diseases, immunosuppression associated with organ transplantation) patients can present as single or multiple masses involving the deep brain. An unusual (e.g. heterogenous or peripheral) enhancement pattern or necrosis is sometimes seen. Rarely, almost a complete lack of mass effect, an infiltrative appearance or the absence of enhancement can be seen with PCNSL in immunocompromised patients.

Locations rarely involved by PCNSL (pituitary, hypothalamus, et al) are also demonstrated in this article.

Comment: nice collection of imaging examples of the wide range of appearances of primary CNS lymphoma.
Volume 3, Issue 1

Title: MR Imaging Findings After Stereotactic Radiosurgery Using the Gamma Knife

Review Type: Article

Category: Neuro-Radiology


Authors: Friedman D, Morales R, Goldman H

Summary:

“Gamma knife” (cobalt-60) radiosurgery (GKR) is an accepted alternative to conventional surgical, medical or radiation therapy management of a range of intracranial pathologic processes.

This pictorial essay presents 30 images (predominantly MR scans) of a range of pathology that can be successfully treated with GKR including thalamotomy for movement disorders, root entry zone or retrogasserian fifth nerve treatment for trigeminal neuralgia, inducing thrombosis within arteriovenous malformations and management of primary and secondary benign or malignant (primary glioma, brain metastasis, eighth nerve schwannoma) neoplasms. Serial imaging over time is shown in several cases emphasizing that lesions may initially appear worse after therapy before regressing.

Comment: Nice examples of a range of pathology are shown. This article barely mentions when to consider using gamma knife radiosurgery as opposed to other treatment modalities and also the potential complications from this type of radiosurgery.
Volume 3, Issue 1

**Title:** Evaluating Pediatric Brain Tumor Cellularity with Diffusion-Tensor Imaging

**Review Type:** Article

**Category:** Neuro-Radiology


**Authors:** Gauvain K, McKinstry R, Mukherjee P, Perry A, Neil J, Kaufman B, Hayashi R

**Summary:**

In an attempt to determine if certain MR characteristics of a lesion can help predict tumor grade, the authors looked at high and low grade pediatric brain tumors (pilocytic astrocytomas, GBMs, anaplastic ependymomas, medulloblastomas, PNETs et al) with respect to tumor and nuclear cellularity (including histologic measurements of total cell cross-sectional cellular area and total nuclear cross-sectional area) and compared these to Apparent Diffusion Coefficient (ADC) and diffusion Tensor imaging (dTi) MR measurements of the same regions acquired pre-operatively.

ADC MR values can be thought of as a measure of how far water molecules can randomly move (Brownian motion) within a given tissue during a given period of time. A high ADC is seen in pure water while lower ADCs are seen in tissues with many membranes, etc. that limit water movement on a molecular level. The authors confirmed previous work that with increased cellularity (which correlates with an increase in tumor grade), ADC values decreased. Specifically, a statistically significant correlation of ADC values with low-grade gliomas and embryonal tumors was seen.

Anisotropy refers to the directionality of diffusion of water molecules within tissue. White matter tracts are anisotropic as water molecules more readily diffuse parallel to these tracts as opposed to perpendicular to these tracts. Isotropy refers to the absence of any directionality of water motion within tissue. Pure water is isotropic (i.e. has no anisotropy) as are extremely cellular processes (that have no preferential "direction" for water molecule movement). In all tumors regardless of grade, the authors found that anisotropy approached zero and could not discriminate among different tumors.
Comment: this article confirms previous work that MR ADC values may correlate with tumor grade (lower ADC suggests higher grade) and that transient changes in anisotropy may be seen as a positive/negative response to therapy before macroscopic changes are seen on conventional MR images.
Volume 3, Issue 1

Title: Diffusion-Weighted MR Imaging of Rim-Enhancing Brain Masses: Is Markedly Decreased Water Diffusion Specific For Brain Abscess?

Review Type: Article

Category: Neuro-Radiology


Authors: Tung G, Evangelista P, Rogg J, Duncan J

Summary:

This small series of 5 rim-enhancing masses on MR scans looked at whether apparent diffusion coefficient (ADC) MR values were specific for abscesses as some authors claim that abscesses have lower ADC values (i.e. are brighter on diffusion imaging and have lower signal on ADC map images) than necrotic tumor masses due to the high "restricted" diffusion of purulent abscess fluid.

Three of the 5 lesions presented by the authors did not represent abscesses. Two were metastatic squamous cell carcinoma lesions and one lesion represented radiation necrosis. The low ADC values in these lesions (similar to that typically associated with abscesses) was postulated to be due to liquefaction necrosis of malignant processes.

While the authors conclude that high signal on diffusion images and low signal on ADC maps reflecting a low ADC is highly suggestive of an abscess, it is not specific for abscess formation and tumor necrosis is not ruled out.

Comment: Diffusion imaging (and ADC maps) can suggest but do not definitively discriminate between abscesses and necrotic neoplasms. More work needs to be done to assess the specificity/sensitivity of ADC measurements with respect to these pathologic processes.
Volume 3, Issue 1

Title: MR Imaging of Pituitary Adenomas After Gamma Knife Stereotactic Radiosurgery

Review Type: Article

Category: Neuro-Radiology


Authors: Tung G, Noren G, Rogg J, Jackson I

Summary:

The authors looked at 44 pituitary macroadenomas treated with gamma knife radiosurgery (GKR) over a follow-up period (mean 36 months) with serial MR studies (a total of 147 contrast-enhanced scans) to attempt to define the expected appearance of response of a pituitary adenoma to GKR over time.

82% of tumors had been previously treated surgically. 50% of tumors were secretory neoplasms. Initial tumor size at initiation of radiosurgery was approximately 6 ccs. 34/44 patients demonstrated reduction in tumor size of at least 25% over the course of this study. Four patients showed no change in tumor size. Mean tumor volume reduction was 9% at 6 months, 24% at 1 year, 34% at 2 years and 50% at 4 years. Six months after surgery a transient increase in the size of tumors was seen in 21% of patients. Decreased enhancement and cyst development did not correlate with changes in tumor volume.

This study confirms previous work that GKR can reduce pituitary macroadenoma tumor volume and that a transient enlargement of a tumor 6 months after therapy is often seen and does not necessarily represent therapy failure.

Comment: Response of pituitary adenomas to gamma knife therapy takes time and follows an expected course. Changes in contrast-enhancement patterns, cyst formation or intratumoral hemorrhage do not appear to correlate with tumor volume changes.
Volume 3, Issue 1

Title: Comparison of Permeability in High-Grade and Low-Grade Brain Tumors Using Dynamic Susceptibility Contrast MR Imaging

Review Type: Article

Category: Neuro-Radiology


Authors: Provenzale J, Wang G, Brenner T, Petrella J, Sorensen AG

Summary: Tumor angiogenesis may correlate with histologic grades of brain tumors. Blood vessel permeability (BVP) is believed to be a marker for tumor angiogenesis. Such permeability can be measured using multiple different MR techniques. The authors compared BVP of high and low grade tumors using a T2*-weighted MR perfusion technique (similar to that used to calculate cerebral blood volume). As nicely demonstrated with images and tables, the authors demonstrate a correlation between tumor BVP on perfusion MR and tumor grade. They also demonstrate (with pathologic proof) that while enhancement is associated with a higher grade of tumor (as conventionally believed), non-enhancing lesions with little mass effect can show permeability changes on perfusion MR that suggest and ultimately correlate with higher grade tumor histology. BVP perfusion MR may prove to be a sensitive marker for glioma grade before conventional MR imaging findings of a high grade lesion (mass effect, enhancement) are seen. However, the authors appropriately caution that little work has been done in this field and that even the association of BVP and tumor angiogenesis and the association between tumor angiogenesis and malignancy remains essentially unproven in humans. If confirmed, BVP perfusion MR maps may be sensitive markers for identifying patients who are early responders or failures to chemotherapeutic and/or anti-angiogenesis therapies. Comment: The authors of this article are careful investigators who are well-respected in the field. Additional work with permeability MR perfusion imaging may indeed confirm their results.

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Volume 3, Issue 1

Title: High-Grade Gliomas and Solitary Metastases: Differentiation by Using Perfusion and Proton Spectroscopic MR Imaging

Review Type: Article

Category: Neuro-Radiology


Authors: Law M, Cha S, Knopp E, Johnson G, Arnett J, Litt A

Summary: The authors retrospectively reviewed a) conventional spin-echo MR, b) contrast-enhanced perfusion MR (pMR) and c) MR spectroscopic (MRS) studies of 51 patients with a solitary brain tumor—33 with high grade primary gliomas and 18 with metastases all of whom had surgery or stereotactic biopsy confirmation of their respective lesions. All patients did not undergo both pMR and MRS evaluation. The area of interest on these studies (where the pMR and MRS evaluations were performed) was the region of “peritumoral edema” (PTE) as defined as the area of abnormal T2 signal surrounding but not including the area of tumor enhancement on contrast-enhanced conventional spin-echo MR (the authors do correctly acknowledge that this region is not truly “peritumoral” in high grade glioma patients as the PTE region does include neoplastic cells in those patients). pMR revealed that the relative cerebral blood volume in the PTE region was significantly (p<.001) higher for high grade gliomas than for metastases. MRS revealed that choline (choline to creatine ratio) was significantly (p<.001) elevated in the region of PTE of gliomas in comparison to that of metastases (no elevation of choline to creatine ratio). The authors conclude that when the conventional spin-echo MR imaging characteristics of high grade gliomas and metastases are similar, such lesions can be differentiated with pMR and MRS. Comment: One can often determine if a solitary brain lesion is a metastasis or primary tumor by reviewing the patient clinical history and/or studying the imaging characteristics of the lesion in question on conventional spin-echo MR. However, it can be difficult to differentiate between the two. It makes sense that studying PTE can help determine the nature of a lesion. When associated with a high grade tumor, the region of PTE will contain some neoplasm (in addition to some vasogenic edema) and therefore some tumor angiogenesis which should be reflected as increased cerebral blood volume on perfusion MR. Similarly, such PTE should demonstrate a neoplastic spectra on MRS. PTE associated with a metastasis almost always represents extensive vasogenic edema which may compress the local microcirculation resulting in decreased regional cerebral blood volume on perfusion MR. In addition, as PTE associated with a metastasis...
rarely reflects spread of tumor, it should not demonstrate a tumor spectra on MRS.

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Volume 3, Issue 1

Title: Morbidity of second-look surgery in pediatric central nervous system

Review Type: Article

Category: Pediatrics/Pediatric Neuro-Oncology


Authors: Raja B Khan, Robert A Sanford, Larry E Kun, Stephen J Thompson

Summary:

The authors retrospectively reviewed 47 consecutive patients at their pediatric hospital over a 13 year period who underwent second-look resections of central nervous system neoplasms. Second look surgery was defined as re-operation for attempted total resection after an initial attempt at total resection (not biopsy alone) at either their or another institution. Low and high grade intrinsic cerebral and spinal cord neoplasms were represented. Peri-operative complications, including new or worsened neurological deficits, and Eastern Cooperative Oncology Group (ECOG) and Lansky functional outcome scores were assessed between 4 and 24 weeks after second-look surgery.

Khan and colleagues report a complication rate of 45%, including 42% new neurological deficits and 15% other complications (hydrocephalus, CSF leak, etc.). Gross total resection (GTR) was achieved in 62% of second-look patients, and near total (NTR) in a further 23%. All patients with low or high grade astrocytomas had GTR or NTR, as did 66% of patients with medulloblastoma. For the group as a whole, there was no change in functional outcome score after second-look surgery. However, patients with early re-operation (< 30 days after initial resection) tended to improve in functional score while those whose re-operation was delayed tended to worsen.

The authors conclude that second-look surgery for central nervous system neoplasm in children is justified, particularly for those tumors in which GTR or NTR has been demonstrated to improve prognosis.
Volume 3, Issue 1

Title: Pediatric spinal tumors

Review Type: Article

Category: Pediatrics/Pediatric Neuro-Oncology


Authors: Uta Schick and Gerhard Marquardt

Summary:

The authors retrospectively reviewed their consecutive, single institution experience over 18 years with pediatric spinal tumors. They surgically treated 34 children (21 M, 13 F) with clinical follow-up from 5 to 117 months (median 26). Mean age at surgery was 12 years. Neurological function was summarized using the Chesire functional scale, ranging from 1 (normal) to 6 (no useful function).

Neurinomas and neurofibromas were the most common tumors (26%) in older children and neuroblastoma and PNET (15%) in younger children. Ependymoma and astrocytoma were the most common intramedullary tumors (60%; 9% of all types). Post-operative neurological status was improved in 68% and worsened in 15%. 53% of patients underwent adjunctive therapy with spinal irradiation and/or chemotherapy. 35% of patients relapsed. 5 patients underwent primary spine stabilization procedures. Five experienced immediate operative complications, two of these requiring further surgery. The authors emphasize the heterogeneous nature of spinal neoplastic disease in children and the need for interdisciplinary medical and surgical management of these complex problems.
Volume 3, Issue 1

Title: Pediatric Craniopharyngiomas: Clinicomorphological Study of 189 Cases

Review Type: Article

Category: Pediatrics/Pediatric Neuro-Oncology


Authors: Zhang YQ, Wang CC, Ma ZU

Summary:

The authors report a single institution, retrospective case series of 189 children (aged 1 to 15 years) with craniopharyngioma. 58% were male. 187 of these patients harbored tumors that were at least partially cystic and all of these proved to be of the adamantinous variety. Two tumors were solid and both proved to be of the squamous papillary variety. 93.1% of tumors demonstrated calcification visible radiologically. The authors identified five distinct anatomical locations at tumor presentation, the most common being retrochiasmal and pre-pituitary stalk (64%). No clinical follow-up data are given to evaluate the various surgical approaches indicated. The authors confirm previous smaller series suggesting a large predominance of cystic, calcified, adamantinous tumors in children with craniopharyngioma.

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Volume 3, Issue 1

**Title:** Radiosurgery for patients with brain metastases: a multi-institutional analysis, stratified by the RTOG recursive partitioning method

**Review Type:** Article

**Category:** Radiation Oncology


**Authors:** Sanghavi SN, Miranpuri SS, et al

**Summary:**

This is an interesting study exploring the role of radiosurgery in patients with brain metastases. Ten institutions pooled the results of their patients with brain metastases that were treated with whole brain radiation followed by a stereotactic boost. The intention was to include boost patients, not those that had failed. The patients in the current series were then compared with the RTOG database in which all of the patients were treated with whole brain without radiosurgery. The RTOG database had been broken down into three prognostic groups (RPA=recursive partitioning analysis). Class I (KPS>70 age <65 controlled primary), class II (all others), and class III (KPS<70).

The study reviewed a total of 552 patients who had an overall median survival of 10.7 months. The authors found that for each RPA class the median survival was superior for patients that received a stereotactic boost. For class I patients the historical control patients had a median survival of 7.1 with the current series having a median survival of 16.1 months. Class II patients had a historical median survival of 4.2 months versus the current series which had a survival of 10.3 months. Finally class III patients improved from 2.3 months to 8.7 months with a stereotactic boost.

The authors also reviewed prognostic factors in general and, not surprisingly, found that patients with higher performance status, controlled primary disease, no extracranial disease, and lower RPA class all had superior survival.

They also found that there was no difference in survival with gamma knife centers versus linear accelerator centers. This study is much larger and a more direct comparison than the phase I RTOG dose finding trial that suggested a potential superiority of gamma knife radiosurgery. There will never be a direct randomized trial comparing linac based treatment and
gamma knife, but this trial is about the best that can be done (it is probably slightly superior to compare in a prospective trial with uniform entry criteria) and it revealed equivalence of the two techniques.

This trial suggests a benefit to stereotactic boost. This is somewhat difficult to reconcile with the RTOG trial reported in abstract that was randomized that did not reveal a benefit in survival to stereotactic boost in patients with 2 or 3 mets (the one met portion remains open). This trial had many more patients and it may be that the RTOG trial was underpowered. It is also possible that in a trial with mets that survival may not be the most valid endpoint as there was improvement in local control, performance status as well as reduced steroid dependence. The other possible explanation may be selection bias in that the authors were better able to select candidate who might have a prolonged survival even though their RPA class was the same.

The study is certainly an interesting one and should be reviewed in conjunction with RTOG 9508, particularly when the single met data becomes available.
Volume 3, Issue 1

**Title:** Stereotactic Radiosurgery and Fractionated Stereotactic Radiotherapy for the Treatment of Acoustic Schwannomas: Comparative Observations of 125 patients treated at one institution

**Review Type:** Article

**Category:** Radiation Oncology

**Journal:** International Journal Radiation Oncology Biology Physics, Vol: 50, No. 5: pages 1265-1278, 2001

**Authors:** Andrews DA, Suarez OS, et al

**Summary:**

This article is interesting for several reasons, but primarily since it is a retrospective review regarding treatment of acoustic schwannomas from an institution which has the capability to perform fractionated radiosurgery as well as conventional radiosurgery utilizing a gamma knife.

They originally had hoped to perform a randomized trial between fractionated therapy versus gamma knife treatment, but secondary to physician or patient preferences were unable to do so and settled for an observational trial.

In the trial, 69 patients were treated with gamma knife and 56 were treated with fractionated radiosurgery on the linear accelerator. Of the 122 patients that were followed the mean follow-up was ~115 weeks for both groups. Tumor control rates were >97% for sporadic tumors on both units. Tumor control was less on both units for NF-2 patients, but there was no statistical difference between the techniques.

Cranial nerve morbidity was low and equivalent for both techniques with the exception of functional hearing preservation. Functional hearing preservation was 2.5 times greater in the patients treated with fractionated stereotactic radiosurgery performed on a linac versus that of patients treated on a gamma knife.

This trial makes a strong argument for fractionated therapy versus single fraction radiotherapy in patients with acoustic schwannomas and functional hearing. This is particularly convincing since all of the patients were treated at the same institution where the expertise and skill used on all the patients...
is presumably equivalent. The one criticism is that the hearing preservation rates are lower (only 33%) in this series than noted in some other gamma knife series. The reason for this is not entirely clear, but the authors hypothesize regarding the dose rate of the cobalt sources as the patients in this trial were treated with fairly new (i.e. high dose rate) sources.

This series appears to support the radiobiologic argument that fractionated therapy should be superior in hearing preservation. It is very unlikely that a randomized trial will ever be performed, so it is not unreasonable to offer fractionated therapy to patients with functional hearing as it is potentially the best available therapy.
Volume 3, Issue 1

Title: The Local Field in Infratentorial Ependymoma: Does the Entire Posterior Fossa Need to be Treated?

Review Type: Article

Category: Radiation Oncology


Authors: Paulino A

Summary:

At first glance this article may appear of interest only to radiation oncologists, however, it should be of importance to all physicians who care for patients, particularly children, with intracranial ependymomas. The evolution of treatment portals for nondisseminated infratentorial ependymoma mirrors the evolution of our understanding of the natural history of the disease, the importance of surgical resection, and developments in radiological imaging which have improved our ability to accurately stage disease at diagnoses.

During most of the 1960s through the 1980s, the "appropriate" treatment volume was the entire craniospinal axis. This was mostly based on the work of Omar Salazar who had demonstrated improved survival for those patients treated with craniospinal irradiation. However, with the development of gadolinium MR allowing for evaluation of the spinal axis, and the results from the Pediatric Oncology Group demonstrating dissemination at diagnosis in only 1 of 37 children with differentiated posterior fossa ependymomas, posterior fossa alone became the target for radiotherapy during the 1990's.

In the article by Paulino, the necessity of full posterior fossa irradiation is questioned. Dr. Paulino reports the patterns of failure, at a median follow-up of 127 months, in 28 patients (median age 12 years) treated at the Children's Hospital of Iowa from 1984-1998. Of the 11 patients who received either CSI or whole brain irradiation, 3 failed--one in the tumor bed, one in the spinal axis, and one synchronously in the spinal axis and non-tumor bed posterior fossa. The two patients who received posterior fossa radiation therapy alone had no evidence of recurrence. Two of the nine patients who received "local field" irradiation (defined as the tumor bed + 2 cm) and 1 of the 6 who were not irradiated developed recurrence in the tumor bed and went on to die of disease. Although no multivariate analysis was performed...
to control for prognostic factors such as extent of resection (this likely would be of little help given the small numbers), the findings are suggestive that treatment to the entire posterior fossa may not be warranted.

It is important to remember that all 4 patients with "high-grade" ependymoma received craniospinal radiation, so in such patients, the results should be interpreted with caution. A more detailed explanation of the "tumor bed" would be of help to radiation oncologists, i.e., was the treatment volume based on MR imaging with gadolinium, was the pre- or postoperative volume used, etc. Additionally of interest would be the information on how the local fields were treated, i.e., with lateral parallel opposed portals or with multiple 3-dimensionally planned fields.

Nevertheless, the article makes an important contribution to directing and defining therapy in these children which could potentially lead to decreased long-term toxicity. If treatment could be delivered to the tumor bed and whole posterior fossa irradiation avoided, structures such as the auditory apparatus could be spared. The most recent CCG study for ependymomas and the current COG trial for ependymomas have used local field irradiation and hopefully long-term follow-up in the children treated on these studies will confirm Dr. Paulino's findings.
Volume 3, Issue 1

Title: A multidisciplinary team approach to skull base chordomas

Review Type: Article

Category: Skull Base Tumors


Authors: Crockard HA, Steel T., et al.

Summary:

Skull base chordomas are rare but have been difficult to manage even in centers of excellence. The authors report a follow-up during the modern imaging era to a previous report from the same center in 1993. This series reports the results of multidisciplinary management of 42 chordomas treated between 1986 and 1998. The mean/median follow-up was 4.25/3.5 yrs. Extent of resection was defined as "complete" if no tumor was seen on post-op MR between 3 and 6 months, "radical excision" if more than 90% was removed and "partial excision" if between 50-90% was removed.

The basic management strategy outlined by the authors included observation for those patients with complete or radical excision, few mitotic figures and KI67 LI less than 6%. All others were treated with 50Gy conventional XRT plus 10-15 Gy radiosurgery boost. 18 of 24 first time patients had radical excision and 1 had complete removal. CSF leaks and new cranial nerve deficits were higher in reoperated patients. The dural penetration rate at surgery was 25% for first time patients (24) and 56% for reoperated patients (18). Surgical mortality for the whole group was 4.2% and 0% for first time patients. Overall survival was 77% at 5 yrs. and 69% at 10 yrs. For patients who achieved complete or radical excision the 5 yr. survival was 100%. The authors noted poorer survival in those patient over the age of 50 and those with KI67 labelling indices above 6%.

This report provides an honest assessment of the limits and problems with surgery for these tumors, especially at reoperation, and stresses a multidisciplinary approach. Surgical neuro-oncologists are urged to read the manuscript in full.
**Volume 3, Issue 1**

**Title:** Analysis of treatment outcome after stereotactic radiosurgery for cavernous sinus meningiomas

**Review Type:** Article

**Category:** Skull Base Tumors


**Authors:** Shin M, Kurita H, et al.

**Summary:**

This report is another with longer term follow-up after radiosurgery for cavernous sinus meningiomas. There were 40 patients followed for a median of 42 months (range 12-123 mo.). Median age was 50.5 yrs. and 28 pts. (70%) had undergone prior resection. At the time of radiosurgery 75% (30 pts.) had cranial nerve deficits, 14 of these related to prior surgery. Treatment was planned in an attempt to deliver 18 Gy to the tumor margin but limits were imposed by the optic apparatus.

Analysis of results was divided on the basis of tumor coverage: Group A total coverage with minimum dose of 14 Gy; Group B more than 90% of tumor covered with minimum 12 Gy and; Group C was only partial coverage. Overall when malignant meningiomas and Group C patients were excluded, the control rate for the remaining 36 patients was 91.3% at 3 years. For Group A the 3 yr. control rate was 100%, 74.6% for Group B and 0% for Group C. 37.5% of tumors were smaller on follow-up imaging at a median time of 11.5 months after radiosurgery.

Factors associated with tumor recurrence were: histologic malignancy, partial treatment, suprasellar extension and extension in more than 3 directions outside the cavernous sinus. Because the control rate with complete coverage at 14 Gy was so good and morbidity acceptable the authors advocate tumor debulking of large tumors with suprasellar or extracavernous extension, followed by radiosurgery.

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Title: Protean Morphology of MRI Abnormalities Following Stereotaxic Radiosurgery

Review Type: Meeting Abstract

Category: Neuro-Radiology

Meeting: Radiological Society of North America, November 25-30, 2001

Summary:

Purpose: To characterize enlarging MRI abnormalities following stereotaxic radiosurgery; and to describe the radiographic nature and clinical significance of these lesions.

Methods and Materials: Fifty-one patients with a variety of brain tumors (number of lesions=101) were treated with stereotaxic radiosurgery at the NIH between 11/98 and 02/01. The average radiosurgery dose equaled 24Gy. In 38 patients (number of lesions=72) MRI scans prior to and after radiosurgery were available for evaluation. T1 and T2-weighted MRI scans were obtained with and without contrast in each case. In 18 patients with 24 tumors enlarging abnormalities within the radiosurgery target volume were observed on follow-up studies. The observation period after treatment ranged from one month to 23 months with a mean of 7.8 months. In five of the treated tumors, histological examination was available and correlated with the imaging findings.

Results: Three distinct patterns of lesion progression were identified on the post-treatment MRI scans: (a) The original enhancing volume corresponding to the treated lesion volume expanded in a homogeneous pattern (11 lesions). (b) A necrotic cavity developed in the center of the lesion, and an irregular enhancing ring was formed, which gradually expanded with time (11 lesions). (c) The original tumor nodule was identified in the post-treatment scans, but a ring of enhancement also appeared around the nodule (2 lesions). Concomitant increase in edema was observed in all cases regardless of the pattern of lesion progression. The increase in the enhancing volume was observed in 12 (67%) of the 18 lesions in which one month post-treatment scans were available. In four patients the initially expanding enhancement eventually decreased in time, and the edema either resolved or diminished considerably. Five additional lesions were subsequently resected and histology revealed post-radiation effects being the dominant feature of the excised specimen. In one patient PET images showed decreased metabolic activity in the treated tumor indicative of...
radiation necrosis, and in another lesion the enlarging abnormality was due to hemorrhage rather than tumor.

Conclusion: Patients treated with radiosurgery may develop progressive MRI abnormalities within the treated volume demonstrating variable patterns of enhancement. Our observation suggests that most of these lesions result from post-radiosurgery effects rather than tumor progression. An adequate period of follow up is required to demonstrate the evolution of these lesions.