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Neurosurgery Concepts

Neurosurgery concepts: Key perspectives on regulatory proteins, management of ossification of the posterior longitudinal ligament, and radiosurgery for intracranial lesions

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THE CD47-SIGNAL REGULATORY PROTEIN ALPHA INTERACTION IS A THERAPEUTIC TARGET FOR HUMAN SOLID TUMORS[7]

Question: Is CD47 a ligand unique to human cancer cells and not expressed on normal human cells? Can anti-CD47 antibody therapy inhibit tumor growth and prevent or treat tumor metastases?

Human tissue specimens were obtained from various tumor types including glioblastoma, ovarian, breast, colon, bladder, hepatocellular carcinoma, and prostate. CD47 expression was analyzed via flow cytometry. CD47 expression was correlated with survival using Kaplan–Meier analysis. An *in vitro* phagocytosis assay was used to assess the ability of anti-CD47 antibodies to enable phagocytosis. *In vivo* experiments were performed to assess the ability of anti-CD47 antibodies to inhibit tumor growth. Tumors were implanted in their native location such that glioblastoma cells were implanted into the left hemisphere of mice. These experiments were performed in both immune-deficient and immune competent mice.

CD47 was highly expressed on nearly all patient tumor samples evaluated including glioblastoma. Tumor cells expressed approximately 3.3-fold more CD47 than corresponding normal cells. High CD47 expression was significantly correlated with decreased progression free and overall survival. In contrast to control experiments, cells treated with antihuman CD47 antibodies were efficiently phagocytosed by both mouse and human macrophages, including glioblastoma neuropsheres. In the mouse xenografts, glioblastoma growth was inhibited by anti-CD47 antibody treatment as compared with controls. This effect was also seen in the other tumor models. Using the bladder carcinoma model, metastases were significantly reduced with anti-CD47 antibody treatment as compared with control. Using the breast cancer model in immune competent hosts, inhibition of tumor growth was inversely correlated with tumor size. The antibody treatment was well tolerated with only self-limited anemia as a side effect.

CD47 is a nonhousekeeping ligand for signal regulatory protein alpha (SIRP-a) that is significantly expressed on a

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wide range of human solid tumors including glioblastoma. CD47 serves as a "don't eat me signal" that through anti-CD47 antibody treatment results in significant reduction in tumor growth both *in vitro* and *in vivo*.

Perspective: A tumors ability to both grow and metastasize is reliant on the tumor cells' ability to avoid phagocytosis by tumor-associated macrophages. This study demonstrates that this "don't eat me" signal is reliant on the interaction between CD47 and SIRP-a. Interrupting this signal displayed a significant reduction in tumor growth and ability to metastasize. Perhaps even more importantly, this treatment was well tolerated with minimal toxicity. The efficacy of this treatment appears to be inversely correlated with tumor size. Consequently, cytoreductive surgery prior to treatment may be of value. Furthermore, treatment with additional antitumor antibodies may be of value in generating a synergistic response. In particular, antibodies that induce cytotoxicity via their effect on macrophages, such as cetuximab, may enhance the ability of anti-CD47 antibodies to induce phagocytosis. Based on this research, Phase I/II clinical trials should be considered using anti-CD47 antibodies including a trial for glioblastoma patients.

THREE-IMENSIONAL MEASUREMENT GROWTH OF OSSIFICATION OF THE POSTERIOR LONGITUDINAL LIGAMENT[2]

Question: Ossification of the posterior longitudinal ligament is a progressive disease, even with surgery. Is there a better modality to measure radiographic progression of disease than the use of serial plain X-rays.

The use of plain radiographs is traditionally used to monitor bony disease progression with time. To better understand the volumetric expansion on bone growth in ossification of the posterior longitudinal ligament (OPLL), the authors used serial thin-slice computed tomography (CT) imaging to develop 3D models of five patients that were sequentially followed. Preoperative and sequential postoperative (laminoplastly) 3D models were superimposed to allow careful analysis of how (and equally importantly, where) bone growth progressed in these five patients. Bony thickness and volume progression were measured in all patients at mean follow-up of 3.1 years (minimum 2 year follow-up). Intra- and interobserver reproducibility was carefully measured to validate their results.

Even following operative decompression, bone growth at the site of the ligament and dorsal vertebral body continues to progress. The three-dimensional imaging system utilizes a voxel-based, quantitative evaluation of both the change in bone thickness and volume. They found that all five patients had at least 0.5 mm or greater progression of heterotopic bone. The mean maximal progression length was 4.7 mm (1.6 mm/year).On average, patients additionally had a 37% (range 18-89%) increase in bony volume during the follow-up period. This correlated to 484 mm/year. Intraobserver reproducibility was high: 0.987.

Despite surgery, ossification of the posterior longitudinal ligament will invariably progress. While previous studies have shown similar progress, the use of plain X-rays limited the radiographic information that could be obtained. The use of multi-detector CT imaging may provide a better 3D understanding of bony progression and a more precise understanding of both dimensional and volumetric growth.

Perspective: While it has been previously demonstrated that bone growth will progress after surgery in OPLL, this has only been studied with plain X-rays. This modality is limited in its ability to evaluate volumetric growth. Further, it only allows evaluation in craniocaudal and mediolateral dimensions. Lastly, certain regions of the cervical spine may be difficult to visualize (especially the low subaxial cervical spine).The use of the author's novel 3D imaging technique allows for a more precise and useful understanding of disease progression in a disease that commonly presents many surgical challenges. Precise 3D information in the postoperative may help aid both postoperative patient guidance and follow-up as well as allows surgeons to make better decisions for their patients.

SURGICAL TREATMENT OF PATIENTS WITH VESTIBULAR SCHWANNOMAS AFTER FAILED PREVIOUS RADIOSURGERY[3]

Question: What is the best treatment option of vestibular schwannoma patients after failed previous radiosurgery?

The authors reviewed the surgical result of vestibular schwannoma who underwent surgery during 10 years. The study cohort was subdivided into group A (radiosurgery prior to current surgery) and group B (partial removal followed by radiosurgery prior to current surgery). The clinical outcomes in the two groups were compared with those in a patient with control group (no previous treatment prior to current surgery, matched characteristics).

There were 15 patients in group A, 13 in group B, and 30 in control group. The authors performed surgery after radiosurgery due to continuous tumor growth and progression of neurologic symptoms. They achieved total tumor removal in all the patients in groups A and B. (96.7% in control group). There were no significant differences in the clinical data including morbidity and complication rate. However, risk of new

cranial nerve deficits and cerebrospinal fluid (CSF) leakage was highest in patients in group B. The rate of anatomical preservation of facial nerve was high in control group (93.3%, versus 86.7% in group A and 61.5% in group B). Facial nerve functional preservation was seen high in control group (87%, versus 78% in group A, 68% in group B).

Complete microsurgical removal of vestibular schwannomas after failed radiosurgery is possible with an acceptable morbidity rate. The functional outcome, however, tends to be worse than in nontreated patients. Surgery after previous partial tumor removal and radiosurgery is most challenging and related to worse outcome.

Perspective: Treatment of vestibular schwannomas after previous radiosurgery is challenging. Although surgery could be considered, the surgical outcomes might not be good due to previous treatments. Many neurosurgeons are unwilling to perform surgery to the patients with previous failed treatment (radiosurgery and/or surgery) due to impact of tissue trauma (adhesnion between tumor and surrounding structures, especially brain stem or cranial nerves). This current study shows acceptable surgical morbidity and complication rate of patients with failed radiosurgery. This study, however, is a retrospective study and the study population is not large enough to generalize their results. Moreover, this study population's patients underwent a surgery by one of the most expert neurosurgeon.

STEREOTACTIC RADIOSURGERY FOR ARTERIOVENOUS MALFORMATIONS AFTER EMBOLIZATION: A CASE-CONTROL STUDY[4]

Question: The authors sought to determine the efficacy of treating arteriovenous malformation (AVM) patients with embolization prior to stereotactic radiosurgery (SRS).

The authors performed a retrospective analysis of 996 patients with AVMs that were treated with SRS between 1987 and 2006.They identified 120 patients who were treated with embolization and SRS for their AVMs. The endpoints used were: Rate of total obliteration, posttreatment hemorrhages, and permanent neurological deficits.

The authors reported that the overall rates of complete AVM obliteration at 3, 4, 5, and 10 years were 35%, 53%, 55%, and 59%, respectively. The rates of hemorrhage for their patients were 0.8%, 3.5%, 5.4%, 7.7%, and 7.7% at 1, 2, 3, 5, and 10 years, respectively. They also reported a rate of permanent neurological deficits at 2.5%.

The authors reported that prior embolization compromised the success of AVM obliteration after treatment with SRS.

Perspective: This study provides long-term follow-up on a large number of AVM patients treated with embolization prior to SRS. The authors found a statistically significant difference in chances for obliteration with patients that were treated with embolization (0 = 0.028). The authors reported that embolization did not increase the risk for hemorrhage, but if one were to embolize, then shrinking the AVM to less than 8 cm^3 would improve the rate of obliteration. While the authors acknowledge the limitations of their study, their findings suggest that we need to reexamine our strategies to approaching large AVMs. They suggest exploring the role of embolization post SRS or to consider staged treatment of SRS.

IS AGGRESSIVE TREATMENT OF TRAUMATIC BRAIN INJURY COST-EFFECTIVE?[6]

Question: Is aggressive treatment of severe traumatic brain injury based on the Brain Trauma Foundation (BTF) guideline cost-effective?

The authors used a decision analytical model to evaluate the outcome and costs of three different management strategies of traumatic brain injuries (TBI), including aggressive management (more than 50% of cases are managed according to the BTF guideline), routine management (less than 50% are managed according to the BTF guideline), and comfort care (one day of intensive care unit (ICU) care followed by care at the medical-surgical unit). Clinical outcome and costs data were extracted from literature reviews, Medicare reimbursement rate and from a prospective database of the authors' group. Quality adjusted life years (QALY) data was calculated based on GOS data using a conversion formula and QALYs were estimated for four age groups (20, 40, 60, and 80 years).

As expected, aggressive care was associated with the highest acute cost and comfort care was associated with the lowest acute cost. However, the outcome of patients with aggressive care was also better, with significantly more patients achieving independent living and returning to work, therefore, when factoring in N the long-term nursing cost and loss of productivity cost, total life time cost was actually lower with the aggressive management strategy for the 20, 40, and 60 year old groups. It was also more cost effective compared with the other two strategies. Even for the 80 year old group, the estimated cost per QALY gained was $88K, which is considered in some research to be below the threshold of being considered cost-effective.

Based on the current model, aggressive treatment management strategy by following the BTF guideline is considered as a highly cost effective strategy for the treatment of traumatic brain injury.

Perspective: In this study, the authors use a decision analytical model to estimate the cost effectiveness of various treatment strategies for severe TBI. Emerging evidence from literature has shown that intensive therapy for TBI is associated with better outcome. Although it is also associated with a higher acute cost, its life time total cost may actually be lower because of lower long-term cost and less loss in productivity. This appears to be applicable not only to the very young patients, but also to older patients as well. This study continues to support an aggressive approach to the treatment of severe TBI, and suggests that it is not only effective, but also cost effective.

SIGNIFICANCE OF SIMPSON GRADING SYSTEM IN MODERN MENINGIOMA SURGERY: INTEGRATION OF THE GRADE WITH MIB-1 LABELING INDEX AS A KEY TO PREDICT THE RECURRENCE OF WHO GRADE I MENINGIOMAS[5]

Question: Does the MIB-1 labeling index provide additional value in predicting tumor recurrence or progression in various Simpson grading subsets following resection of WHO Grade I meningioma?

A retrospective review of 685 patients operated on for intracranial meningiomas over a 15-year period were reviewed. Only patients with World Health Organization (WHO) Grade I meningiomas were included in the analysis, with a minimum of 6 months follow-up. Patients with neurofibromatosis, prior radiation or multiple surgeries were excluded from the analysis.

Two-hundred and forty patients with 248 WHO Grade Imeningiomas were included in the analysis. Extent of resection was correlated with tumor location. Five-year recurrence-free survival (RFS) after Simpson Grade I, II, III, and IV resections were 97.6%, 87.7%, 84.1%, and 56.8%, respectively. Although a Simpson Grade of IV correlated significantly with RFS, no statistically significant correlation was borne out among Simpson Grades I-III in predicting RFS. Only one patient with a Simpson Grade I tumor had recurrence over the follow-up period. Among patients with Simpson Grades II and III, a MIB-1 labeling index >3% was significantly correlated with lower RFS. In addition, a multivariate analysis using a Cox proportional hazard model for Simpson Grade II and III resections demonstrated that the MIB-1 LI was the single significant predictor of recurrence (Odds ratio (OR) 4.65, 95% confidence interval (CI) 1.59-14.0; $P = 0.006$).

In subtotally resected WHO Grade I meningiomas, the Simpson Grading System correlates with recurrence in Grade IV resections, but may be limited in predicting recurrence among Grade II and III resections. Routine incorporation of MIB-1 labeling index immunostaining, however, improves the predictive value of recurrence if the MIB-1 index is greater than 3% in Simpson Grade II and III resections.

Perspective: The ability to risk stratify patients with benign intracranial tumors for recurrence is important, and as demonstrated by Oya, *et al.*, is contingent on more than the intraoperative degree of resection in subtotally resected meningiomas. Tumor progression is associated with the MIB-1 labeling index, which can be used to identify patients who are at higher risk for recurrence, even among benign WHO Grade I tumors. This lends support to obtaining routine MIB-1 immunostaining, and more recently molecular and genomic profiling, for subtyping intracranial tumors and improving our ability to stratify tumor subsets based on behavior and the propensity for progression.

ADULT GLIOBLASTOMA MULTIFORME SURVIVAL IN THE TEMOZOLOMIDE ERA: A POPULATION-BASED ANALYSIS OF SURVEILLANCE, EPIDEMIOLOGY, AND END RESULTS REGISTRIES[1]

Question: Has survival for patients diagnosed with Glioblastoma (GBM) increased after the use Temozolomide in the United States?

Data from 19,674 GBM cases, aged 20 years or greater, diagnosed between 1993 and 2007 in the populations-based Surveillance, Epidemiology, and End Results Program (SEER) database were collected. Proportional hazards models were used to calculate calendar period hazard ratios (HR) and 95% CI, adjusted for demographic covariates. Survival across periods was compared using the Kaplan–Meier method.

There was a progressive decrease in HRs when comparing cases diagnosed between 1993 and 1995 to cases diagnosed between 1999 and 2001.The multivariate-adjusted HR for 2005-2007 versus 1993-1995 was 0.69 (95% CI, 0.65-0.72). Age-stratified analyses revealed that this progressive decrease occurred in all age groups except for patients greater than 80 years of age. Two-year survival increased from 7% among cases diagnosed in 19931995 and 19961998 to 9% among cases diagnosed in 1999-2001, 13% in 2002-2004, and 17% in 2005-2007. The disparity in survival between young and old patients increased in the temozolomide era, with 2-year survival of 39% among cases diagnosed at ages 20-44 years and 1% among cases diagnosed at 80+ years in 2005-2007.

Using the SEER database, there was a modest but meaningful population-based improvement in survival

of GBM patients. This is likely due to the widespread use of temozolomide although other advances like improvements in gross total resection could also play a role.

Perspectives: It is commonly said that there have been no advances in the treatment of patients diagnosed with GBM. This manuscript suggests that the survival of GBM patients over the past decade since the use of temozolomide has increased. It is important not only to evaluate the median overall survival of these patients, but to look at percent of patients alive at certain time points as well as looking at certain subclasses of patients. For example, the survival in patients aged over 80 years has not significantly improved. In addition, this manuscript has nice tables, breaking patients into different ages as well as treatment received and the corresponding median overall survival and 2 year survival for each of these groups.

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