Neurosurgery Concepts: Perspectives on Key Articles in Neurosurgery

Neurosurgery concepts

Isaac Yang, Jin Mo Cho1, Chaim B. Colen2, Gordon Li3, Michael Lim4, Jonathan H. Sherman5, Vincent Yat Wang6

Departments of Neurosurgery, UCLA, Los Angeles, California, USA, 1Ajou University School of Medicine, Suwon, South Korea, 2Beaumont Hospital, Grosse Pointe, Michigan, 3Stanford University, Stanford, California, 4Johns Hopkins, Baltimore, Maryland, 5George Washington University, Washington, DC, and 6UCSF, San Francisco, California, USA

E-mail: *Isaac Yang - iyang@mednet.ucla.edu; Jin Mo Cho - chojinmo@gmail.com; Chaim B. Colen - chaim.colen@gmail.com; Gordon Li – gordonli@stanford.edu; Michael Lim - mlim3@jhmi.edu; Jonathan H. Sherman - jsherman0620@gmail.com; Vincent Yat Wang - WangV@neurosurg.ucsf.edu

*Corresponding author

Received: 1 November 11 Accepted: 4 November 11 Published: 30 November 11

This article may be cited as: Yang I, Cho JM, Colen CB, Li G, Lim M, Sherman JH, et al. Neurosurgery concepts. Surg Neurol Int 2011;2:173.

Available FREE in open access from: http://www.surgicalneurologyint.com/text.asp?2011/2/1/173/90444

Copyright: © 2011 Yang I. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Senft C, Bink A, Franz K, Vatter H, Gasser T, Seifert V. Intraoperative MRI guidance and extent of resection in glioma surgery: A randomised, controlled trial. Lancet Oncol. 2011 Oct;12(11): 997-1003.

Study Question: Does intraoperative MRI enhance the extent of resection for glioma surgery?

Methods: Fifty-eight adult patients with enhancing tumors amenable to gross total resection were enrolled in a prospective, randomized, parallel group trial for glioma neurosurgery. All preoperative and postoperative imaging were reviewed by a blinded neuroradiologist, and the patients were prospectively blinded in this randomized 1:1 clinical trial.

Results: Nine patients in this randomized trial were withdrawn mostly due to having a non-glioma metastasis. The intraoperative MRI group was associated with a significant increase in tumor resection (96% vs. 68%, P = 0.023). There was no difference in the morbidity and complications between the MRI and control groups. Twenty-two patients in each group had grade 4 glioblastoma, and the median preoperative tumor volume was similar in both the groups (17.7 cm³ vs. 21.1 cm³). Of the total patients evaluated with intraoperative MRI, 33% were led to extended tumor resection due to the addition of this technique. This study also analyzed senior surgeon and junior surgeon experience and found that it did not make a significant difference for the extent of resection. Lastly, the greater extent of resection was associated with a trend toward improved survival, but this was not statistically significant (226 days vs. 154 days, P = 0.087). Patients with residual tumor had the shortest progression-free survival.

Conclusions: In a randomized, prospective trial, intraoperative MRI may be associated with improved extent of resection.

Perspective: This prospective, randomized trial demonstrates in a select and small population that intraoperative MRI may be helpful in achieving greater extent of resection. Furthermore, this study contributes to the mounting evidence that increased extent of resection may be associated with improved survival outcomes. Further analysis of incorporating technology to improve the extent of resection must be achieved to improve our clinical outcomes. Finally, our understanding of glioma must also evolve, as the tumor is likely extending beyond areas of contrast enhancement on the MRI.

Summary written by: Isaac Yang, M.D.

Sanai N, Polley MY, McDermott MW, Parsa AT, Berger MS. An extent of resection threshold for newly diagnosed glioblastomas. J Neurosurg 2011;115:3-8.

Study Question: What proportion of contrast-enhancing tumor must be resected to obtain a survival advantage in...
glioblastoma patients and how much does this survival advantage increase beyond this resection threshold?

Methods: The authors assessed 500 consecutive patients with newly diagnosed supratentorial glioblastoma over a 12-year period. In this analysis, the authors analyzed clinical, radiographic (including MR imaging-based volumetric tumor analysis), and outcome parameters.

Results: The median age of the 500 patients was 60 years, with a median Karnofsky performance scale (KPS) of 80. The median preoperative tumor volume was 65.8 cm³ and the median postoperative tumor volume was 2.3 cm³, equating to a 96% median extent of resection. Via a multivariate Cox proportional hazards analysis, postoperative tumor volume (P < 0.0001), extent of resection (P = 0.004), KPS (P = 0.001) and age (P < 0.0001) were predictors of overall survival. A significant survival advantage was seen with a minimal extent of resection of 78% with a 12.5-month median survival. Survival increased to 12.8 months with >80% resection, 13.8 months with 90% resection, and 16 months with 100% resection.

Conclusions: In newly diagnosed glioblastoma patients, aggressive resection leads to improved overall survival. This survival advantage is seen with the extent of resection as low as 78%.

Perspective: Previous studies have displayed efficacy with regard to improved overall survival in glioblastoma patients with greater extent of resection. One study of note reported that to obtain this survival advantage, the surgeon must resect >98% of the enhancing tumor. The current study draws into question this previous all-or-none philosophy displaying efficacy with the extent of resection as low as 78% via their analysis with a homogenous patient population. Perhaps even more important, this study draws into question the role of resection in patients with either large tumors in eloquent cortex or bi-hemispheric tumors where a significant resection is not possible without significant morbidity. As seen in previous reports, this study displays the importance in KPS in overall survival and helps further clarify which patients should have a biopsy alone and which patients should undergo radical resection.

Summary written by: Jonathan H. Sherman, M.D.

Panczykowski DM, Tomycz ND, Okonkwo DO. Comparative effectiveness of using computed tomography alone to exclude cervical spine injuries in obtunded or intubated patients: Meta-analysis of 14,327 patients with blunt trauma. J Neurosurg 2011;115:541-9.

Study Question: Is multi-slice helical computer tomography scan of the cervical scan alone sufficient to exclude an acute, unstable cervical spine injury in obtunded or intubated patients?

Methods: The authors performed a systemic review and meta-analysis. Studies that met inclusion criteria were those that compared modern CT (<3 mm thickness) with plain radiography, MR imaging, or dynamic fluoroscopy and had data regarding the acute traumatic findings and treatments for unstable injuries. Data analyzed included patient characteristics, diagnostic protocols, and outcome data including injury detected and treatment descriptions.

Results: Seventeen studies met inclusion criteria. A total of 14,327 obtunded or intubated patients with blunt injury were included in the study. Thin slice CT scan (median thickness 2 mm) was compared to radiographs, MRI, dynamic fluoroscopy or a combination of modalities. A total of 7 patients had injuries that were missed by CT scan and required additional interventions such as surgery or cervical collar. Only three of those patients were deemed to have an unstable injury. The overall negative likelihood ratio of an unstable cervical spine injury after a negative CT scan for acute injury was less than 0.001, and the negative predictive value of a normal CT scan was 100%.

Conclusion: Thin slice CT scan of the cervical spine is sufficient to rule out a significant unstable cervical spine injury in obtunded or intubated trauma patients.

Perspective: In obtunded or intubated patients, it is not possible to clear a cervical spine for acute injury through clinical exam alone. In most trauma centers, CT scan is the primary screening tool for cervical spine injury, given its speed, sensitivity and specificity. While CT scan evaluates osseous structures well, it is not sufficient to diagnose soft tissue injuries like ligamentous or intervertebral disc injury. Therefore, there is a theoretical risk of a missed soft tissue injury that results in an unstable spine. Data from this study show that the risk of missing an unstable cervical spine injury after a negative CT scan is extremely small, compared to the complications of continual wearing of the cervical collar and transport to the MRI scanner. Therefore, the data here support early removal of the cervical collar if CT scan of the cervical spine is negative.

Summary written by: Vincent Y. Wang, M.D., Ph.D.

Sampson JH, Aldape KD, Archer GE, Coan A, Desjardins A, Friedman AH, et al. Greater chemotherapy-induced lymphopenia enhances tumor-specific immune responses that eliminate EGFRvIII-expressing tumor cells in patients with glioblastoma. Neuro Oncol 2011;13:324-33.

Study Question: Does myelosuppression secondary to Temozolomide (TMZ) potentiate or limit EGFRvIII
peptide vaccine induced anti-tumor immunotherapy in glioblastoma (GBM) patients?

Methods: Adults with newly diagnosed GBM were eligible for the clinical trial if they met the following criteria: 1) gross total resection of their tumor followed by standard conformal beam radiotherapy with concurrent TMZ, 2) EGFRvIII expression via immunohistochemistry (IHC), 3) Karnofsky Performance Scale (KPS) of >70, and 4) no radiographic evidence of recurrence after irradiation. Patients were vaccinated with a peptide that spans the EGFRvIII mutation (LEEPKCNYYVTDHC) conjugated to keyhole limpet hemocyanin (PEPvIII-KLH; BioSynCorporation) along with granulocyte-macrophage colony-stimulating factor (GM-CSF), starting within 6 weeks of completing radiation. Patients were sequentially assigned to receive TMZ at a standard (STD) targeted dose of 200 mg/m² for the first 5 days of a 28-day cycle (n = 12) or at a dose-intensified (DI) targeted dose of 100 mg/m² for the first 21 days of a 28-day cycle (n = 10).

Delayed-type hypersensitivity (DTH) reactions were assessed within 48–72 h by a positive skin test defined as 0.5 mm induration. Humoral responses were compared based on maximum titer obtained as measured by enzyme-linked immunosorbent assay (ELISA) testing from the serum. Immunostaining for EGFRvIII was performed on paraffin-embedded tissue specimens before enrollment and at progression. Absolute and subset leukocyte counts were quantified by flow cytometry using a direct immunofluorescence.

Results: Toxicity was minimal and limited to possible allergic reactions in 4 of 22 patients. There were no autoimmune reactions or T2 changes on the MRI. One subject was removed because of the allergic reaction. Patients receiving the STD 5-day schedule exhibited at least transient grade 2 lymphopenia by the 4th cycle of TMZ. Grade 3 lymphopenia was observed in only two patients with this regimen at any time point. Sustained grade 2 lymphopenia was induced in all patients receiving the DI schedule by the 4th cycle of TMZ, and by the 6th cycle of TMZ, all patients exhibited a sustained grade 3 lymphopenia. B-cell counts increased in the STD cohort, but they were significantly reduced in the DI cohort (P = 0.004; paired t-test). TMZ treatment did not lead to a significant reduction in the proportion of Treg in the STD cohort (P = 0.134; paired t-test), but there was an increase in the proportion of Treg at vaccine 6 within the DI cohort (P = 0.008). No patient had evidence of EGFRvIII cellular or humoral immunity prior to vaccination. All patients exhibited EGFRvIII-specific humoral responses by vaccine 8 (P < 0.0001). The antibody titers were unexpectedly higher in the DI cohort when compared to the STD cohort despite worse lymphopenia (L:634,982 compared with L:186,521; P = 0.037). When evaluated at vaccine 8, none of the STD cohort developed a DTH reaction, but 7 of 8 in the DI cohort did. Histologic samples from 12 of 17 recurrent tumors were available for EGFRvIII expression IHC analysis. Eleven of these samples had lost expression of EGFRvIII (P < 0.0001; binomial proportions). There was no difference in progression-free survival (PFS) or overall survival (OS) between the DI and STD cohort, but the study was not powered to detect such differences. The median PFS of all patients was 15.2 months (CI95: 11.0–18.5 months), the median PFS from the time of vaccination was 11.8 months (CI95: 8.1–15.6 months), the OS from the time of diagnosis was 23.6 months (CI95: 18.5–33.1 months) and the median OS from the time of vaccination was 19.3 months (CI95: 15.6–30.7 months). After adjustment for age and KPS, the risk of death of the vaccinated patients was significantly lower than observed in the TMZ-treated historical control group.

Conclusions: Despite profound lymphopenia and increase in Treg cells, both humoral and cellular vaccine-induced immune responses are enhanced by the DI TMZ regimen. Furthermore, vaccination of these patients resulted in elimination of expression of the EGFRvIII antigen and was significantly associated with increase in PFS and OS.

Perspectives: Postoperative radiation with concurrent chemotherapy followed by maintenance chemotherapy is the standard of care for GBM patients. The current study gives evidence that TMZ-induced lymphopenia does not inhibit EGFRvIII peptide vaccine-induced immune responses in GBM patients. Instead, the DI TMZ regimen which leads to increase in lymphopenia, decrease in B cells and increase in Tregs seems to potentiate the vaccine-induced immune response. These results suggest that concurrent use of myelosuppressive chemotherapy can be given effectively with vaccine therapy and this does not inhibit the induction of the desired immune response. Furthermore, these results suggest a possible survival benefit for GBM patients treated with the EGFRvIII peptide vaccine. A randomized, controlled clinical trial is currently being planned to further study this question.

Summary written by: Gordon Li, M.D.

Kotloski R, Lynch M, Lauersdorf S, Sutula T. Repeated brief seizures induce progressive hippocampal neuron loss and memory deficits. Prog Brain Res 2002;135:95-110.

Study Question: Do repeated brief seizures worsen memory deficits in rats?

Methods: Kindled rats that experienced a range of three afterdischarges to 134 secondary generalized tonic-clonic (Class V) seizures evoked by stimulation of the
olfactory bulb were evaluated in a radial arm maze task that is a measure of spatial memory and is disrupted by hippocampal damage. After completion of the memory task and a minimum of ~3 months after the last evoked seizure, stereological methods were used to assess neuronal populations at septal and temporal locations of the hippocampus and dentate gyrus.

**Results:** Repeated brief seizures induced a long-lasting deficit in spatial memory performance that was detected after a cumulative total of ~6 partial and 30 secondary generalized seizures. The memory deficit progressively increased as a function of the number of seizures, and was not observed in age-matched, electrode-implanted, unstimulated, but otherwise similarly handled paired controls. Neuronal loss was detected in the temporal hilus of the dentate gyrus, CA1, and CA3 of the hippocampus after 69 or more secondary generalized tonic–clonic seizures, and was associated with the progressive memory dysfunction.

**Conclusions:** Hippocampal sclerosis and associated memory dysfunction are induced by repeated seizures and imply that seizure control could prevent adverse long-term consequences of seizures on hippocampal dependent functions.

**Perspective:** Kotloski et al. assessed the long-term effects of repeated brief seizures on spatial memory and hippocampal neuronal populations in kindled rats. The authors found that repeated brief seizures induced progressive, permanent functional injury to hippocampal neurons, which produced spatial memory deficits accompanied by gradually evolving neuronal loss in a pattern resembling human hippocampal sclerosis.

Summary written by: Chaim B. Colen, M.D., Ph.D.

**Borg N, Guilfoyle MR, Greenberg DC, Watts C, Thomson S. Serum albumin and survival in glioblastoma multiforme. J Neurooncol 2011;105:77-81.**

**Study Question:** Is serum albumin level of prognostic value in glioblastoma multiforme (GBM) patients?

**Methods:** The authors examined 685 patients with histologically proven GBM. They compared a hypoalbuminemia group with a normal level albumin group by statistical methods.

**Results:** Postoperative survival was significantly less for patients in hypoalbuminemia group (<30 g/l, n = 82) than for those in normal albumin level group (median 2.3 vs. 5.6 months, \( P < 0.001 \) logrank test). Also, lower normal albumin (30–40 g/l, n = 371) had significantly shorter survival compared against patients with albumin in the upper normal range (40–50 g/l, n = 96) (median 5.1 vs. 8.8 months, \( P < 0.001 \)). Multivariate Cox regression showed the independent predictors of survival to be age, debulking surgery, chemoradiotherapy, and serum albumin (Hazard Ratio 0.97 per g/l, \( P < 0.005 \)).

**Conclusion:** Preoperative serum albumin level is a significant predictor of survival in patients with GBM.

**Perspective:** Although serum albumin level has been established as an important prognostic indicator in other malignant diseases, it has not been notable in central nervous system disease. This study’s results suggest that hypoalbuminemia may negatively affect the prognosis of GBM patients. If these retrospective observational data are established by a prospective study, serum albumin could be a useful prognostic indicator for GBM patients.

Summary written by: Jin Mo Cho, M.D.