Neurosurgery Concepts

Perspectives on key articles in neurosurgery

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Hansasuta A, Choi CY, Gibbs IC, Soltys SG, Tse VC, Lieberson RE, et al. Multisession stereotactic radiosurgery for vestibular schwannomas: Single-institution experience with 383 cases. Neurosurgery 2011;69:1200-9.

Study Question: What is the tumor control and complication rate of multisession stereotactic radiosurgery for the treatment of vestibular schwannomas?

Materials and Methods: Three hundred and eighty-three patients with vestibular schwannomas treated with CyberKnife stereotactic radiosurgery at Stanford University Medical Center between 1999 and 2007 were retrospectively reviewed. Ninety percent of the cases were treated with 18 Gy in three sessions.

Results: Three- and five-year Kaplan–Meier tumor control rates were 99% and 96%, respectively, with a median follow-up of 3.6 years (1–10 years). For tumors <3.4 cm³, the 5-year control was 98%. Neurofibromatosis type 2 tumors were associated with worse tumor control (P = 0.02). In 200 patients who had serviceable hearing prior to the treatment (Gardner–Robertson grade 1 and 2), the crude rate of serviceable hearing preservation was 76%. Smaller tumor volume was associated with hearing preservation (P = 0.001). There was no case of post-treatment facial weakness. Eight patients (2%) developed trigeminal dysfunction, half of which was transient.

Conclusions: Multisession stereotactic radiosurgical treatment of vestibular schwannomas results in an excellent rate of tumor control. The hearing, trigeminal nerve, and facial nerve function preservation rates reported are promising.

Perspectives: Surgical resection of vestibular schwannomas can lead to multiple complications. Stereotactic radiosurgery has been shown in many retrospective series to have good tumor control rates with minimal complications. Most of these series have been single-session radiosurgery series, and some believe that a multi-session approach could further minimize the radiosurgical complications. This current series is the largest series of vestibular schwannoma patients treated with multi-session stereotactic radiosurgery. The control rate is excellent, there were no instances of facial nerve injury, and the hearing preservation rate is also excellent. This series, however, is a retrospective study. A head to head randomized study between single versus multi-session stereotactic radiosurgery needs to be done.

Summary written by: Gordon Li, MD
Hofmann BM, Höllig A, Strauss C, Buslei R, Buchfelder M, Fahlbusch R. Results after treatment of craniopharyngiomas: Further experiences with 73 patients since 1997: Clinical article. J Neurosurg 2011. [In press]

Study Question: Do surgical experience and recent advances in neuroimaging and surgical technique improve outcomes in patients with craniopharyngioma?

Materials and Methods: A retrospective chart review of 73 patients operated on with newly diagnosed craniopharyngioma was conducted. Patients underwent some combination of cyst aspiration, transsphenoidal surgery, or open craniotomy. Results were compared to a previous cohort by the same senior author, which spanned from 1983 to 1997. A paradigm shift in the authors’ strategy has prompted attempts toward more complete surgical resection, even at the expense of endocrinological dysfunction, with care to preserve visual, cognitive, and neurological function.

Results: The mean follow-up time for this cohort of 73 patients was 25 months. Eight patients had pure stereotactic cyst aspiration performed on account of hypothalamic invasion and/or patient age. Other surgical approaches included: transsphenoidal (23 patients), frontolateral (11 patients), subfrontal (27 patients), and transventricular (1 patient). A multi-step approach was undertaken in 23 patients.

Gross-total resection (GTR) was achieved in 88.5% of cases in which a transsphenoidal approach was used and 79.5% of those in which a transcranial approach was used (85.2% of those in which a subfrontal approach was used and 72.7% of those in which a frontolateral approach was used). In the total series, GTR was achieved in 83.1% of cases (vs. 49.3% in the authors’ former series). The complication rate was 13.8% without any mortality. New endocrine deficits were observed more frequently in patients treated with transcranial approaches over the years (16.3–66.7% vs. 2.6–50.0%), but were less frequent after transsphenoidal approaches (5.2–19.2% vs. 2.9–45.7%). In the total series, complications were observed in nine cases (complication rate 13.8%). Four patients suffering from CSF leakage (6.2%) required further surgical treatment; severe sinusitis, wound healing problems, and meningitis each occurred in 1 (1.5%) patient. Two (3.1%) patients experienced a deterioration of visual function.

Conclusions: Advancements in surgical technique and accumulated surgical experience can improve outcomes in patients with craniopharyngioma. A multi-step strategy may be required to optimize outcomes in these patients. Selection of the ideal surgical approach is a key factor in improving outcomes, with hypothalamic deficiencies being a key issue in the treatment of patients with craniopharyngiomas. In patients with preexisting hypothalamic deficiencies, pretreatment (medical treatment or stereotactic cyst aspiration) may be performed prior to open surgery because preexisting deficiencies are associated with an increased risk for deterioration of these functions.

Perspective: The excellent results from one of the most experienced centers in treating craniopharyngiomas are presented. The improvement in the authors’ outcomes pertaining to GTR as compared to their previous series and very low complication rates demonstrate the value of experience and judgment in selecting a surgical approach as it pertains to the treatment of these tumors. Endocrine dysfunction, a replaceable byproduct of aggressive craniopharyngioma resection, may be justified if the potential for GTR exists, although restraint is warranted in tumors invading the hypothalamus.

Summary written by: Gabriel Zada, MD

Khayal IS, Vandenbeng SR, Smith KJ, Cloyd CP, Chang SM, Cha S, et al. MRI apparent diffusion coefficient reflects histopathologic subtype, axonal disruption, and tumor fraction in diffuse-type grade II gliomas. Neuro Oncol 2011;13: 1192-201.

Study Question: Does an MRI ADC-based criterion to distinguish between grade II oligodendroglioma and astrocytomas hold for an independent set of grade II gliomas that include 1p/19q co-deleted and intact oligoastrocytoma? Is MRI ADC associated with tumor microstructure?

Materials and Methods: The authors assessed 30 patients with diffuse grade II gliomas including oligodendroglioma, astrocytoma, and oligoastrocytoma. Conventional MRI was performed with a 3T magnet. Using DTI data, normalized ADC (nADC) histograms were performed for each patient. Within the non-enhancing lesion, median nADC values greater than or equal to 1.8 were marked as blue and median nADC values less than 1.8 were marked in pink. Based on previous data, the former was used as a criterion for astrocytoma and the latter was used as a criterion for oligodendroglioma. 1p/19q intact oligoastrocytomas were considered as astrocytoma and 1p/19q co-deleted oligoastrocytomas were considered as oligodendroglioma. nADC-guided biopsies were then taken. The SMI-31 immunohistochemical stain was used to assess neuronal process loss and disruption.

Results: Two to three biopsies were available for each patient, with a total of 45 nADC-guided biopsies available from 21 of 30 patient specimens. Using the median nADC value, oligodendroglioma could be differentiated from astrocytoma with 91% sensitivity and 92%
specificity. For the oligoastrocytomas, oligodendroglioma-like gliomas were distinguished from astrocytoma-like gliomas with 95% sensitivity and 95% specificity. nADC values were higher in the high tumor fraction biopsies than the low tumor-fraction biopsies (P = 0.004). The authors also identified a significant positive association between nADC value and the SMI-31 axonal disruption score (P = 0.008). In looking at histopathologic subtype, a positive association was observed between nADC and SMI-31 in astrocytoma-like biopsies (P = 0.055).

Conclusions: The authors’ previously determined median nADC threshold of 1.8 can be used to differentiate between grade II oligodendroglioma and astrocytoma. This association is also true for both 1p/19q intact and co-deleted oligoastrocytoma. The nADC is also associated with both the fraction of tumor cells and the degree of axonal disruption.

Perspective: In recent literature, there exists a high interest in identifying non-invasive modalities that can be utilized to provide prognostic information to patients. As oligodendroglioma displays a more favorable prognosis than astrocytoma, an imaging modality that can differentiate between the two types of non-enhancing low-grade gliomas can be of value prior to a definitive biopsy or surgical resection. Specifically, the authors argue that the median nADC is a useful prognostic tool for unresectable non-enhancing tumors. This prognostic value also holds when comparing 1p/19q deletion status, which is known to have prognostic value in and of itself. The authors’ conclusion that nADC is valuable as a non-invasive prognostic marker is perhaps shortsighted as definitive histology still serves as the primary data point that clinicians use to determine treatment. Similar to the use of PET scan imaging for determining biopsy sites, the nADC perhaps can be even more valuable in localizing ideal biopsy sites for accurate diagnosis of these lesions. As treatment is dictated by the biopsy specimen with the highest grade, such information provided by the nADC can help to maximize the diagnostic potential of the stereotactic biopsy. This information can assist clinicians in not only providing prognostic information to patients but also determining the most appropriate treatment.

Summary written by: Jonathan H. Sherman, MD

Oddo M, Levine J, Mackenzie L, Frangos S, Feihl F, Kasner S, et al. Brain hypoxia is associated with short-term outcome after severe traumatic brain injury independently of intracranial hypertension and low cerebral perfusion pressure. Neurosurgery 2011;69:1037-45.

Study Question: Is brain hypoxia, as measured by partial pressure of oxygen in brain tissue (PbtO2), associated with worsened outcome in patients with severe traumatic brain injury (TBI) and is this relationship independent of intracranial hypertension or low cerebral perfusion pressure (CPP)?

Materials and Methods: This is a retrospective analysis of prospectively collected data from a prospective observational database. One hundred and three patients were included in this study. Duration of brain hypoxia (PbtO2 < 15 mmHg), intracranial hypertension (intracranial pressure [ICP] > 20 mmHg), low CPP (<60 mmHg), as well as clinical and demographic data, were studied for their association with outcome within 30 days of injury.

Results: Out of the 103 patients, 55 suffered brain hypoxia, with a mean duration of 8.6 hours. Seventy-four patients experienced intracranial hypertension and 75 patients had episodes of low CPP. Causes or conditions associated with brain hypoxia were identified in majority of the cases. Low CPP/high ICP were found in about 50% of brain hypoxia episodes, and low CPP/low MAP were noted in about 25% of the episodes. Other factors, such as fever, induced cooling, low PaO2, and hemoglobin below 9 g/dL, were also associated with brain hypoxia episodes. While patients with elevated ICP or low CPP were more likely to have episodes of brain hypoxia, brain hypoxia was also found in patients with normal CPP (9 of 27) and ICP (12 of 28). In univariate analysis, age, admission GCS, Marshall CT score, APACHE II score, high ICP, and brain hypoxia, but not low CPP, were noted to be associated with short-term outcome. In a multi-variable analysis, only Marshall CT score, admission GCS, APACHE II score, and brain hypoxia, but not elevated ICP, were found to be independent predictors of outcome.

Conclusion: Brain hypoxia is associated with poor short-term outcome in severe TBI patients and this association is independent of elevated ICP, low CPP, or injury severity.

Perspective: Management of severe TBI patients remains a challenge in neurotrauma. Most of the current management strategies, as outlined in the Brain Trauma Foundation guidelines, aim to control ICP and in maintaining an adequate CPP. PbtO2 monitoring has been used more extensively in the intensive care unit as an adjunct monitor for severe TBI patients. In this study, as well as others, it is becoming clear that brain hypoxia is associated with poor outcome. How to use PbtO2 monitoring data to guide therapy, however, is still unclear. As noted in this study, most of the brain hypoxia episodes are associated with either high ICP and/or low CPP. According to the guidelines, such patients or episodes will be treated regardless of their PbtO2. The most interesting group of patients is the one with brain hypoxia but normal ICP and CPP. The authors implied that these patients were treated with elevation of their CPP using pressor, but the details were not available. Were some
of these patients’ CPP pushed above 70 mmHg? Was there a limit of the upper CPP? Similarly, other factors that affect PbtO₂, such as temperature control, transfusion threshold, and PaO₂, are all known to have some effect on the outcome of TBI patients. However, the optimal temperature, transfusion threshold, and oxygenation remain an active area of research right now.

Undoubtedly, PbtO₂ monitoring and PbtO₂-guided therapy have a significant role in the management of severe TBI patients. The decision of whether to use an ICP-guided, CPP-guided, PbtO₂-guided therapy, or a combination of all three probably needs to be individualized for each patient. Further studies on identifying the patient group that will benefit from a PbtO₂-guided therapy strategy will be important to develop management strategy of a patient with severe TBI.

Summary written by: Vincent Y. Wang, MD, PhD

Hasegawa T, Kida Y, Kato T, Iizuka H, Yamamoto T. Factors associated with hearing preservation after Gamma Knife surgery for vestibular schwannomas in patients who retain serviceable hearing. J Neurosurg 2011;115:1078-86.

Study Question: Is radiosurgery a better option for patients who have small vestibular schwannomas with serviceable hearing?

Materials and Methods: The authors reviewed the patients with Gardner–Robertson (GR) Class I or II serviceable hearing and vestibular schwannomas (VSs) treated with Gamma knife surgery (GKS) between 1991 and 2009; 117 were evaluable via periodic MR imaging and audiometry. In this analysis, the authors analyzed the factors related with hearing preservation after GKS.

Results: Fifty-six patients (48%) had GR Class I hearing and 61 (52%) had GR Class II hearing at the time of GKS. The median tumor volume was 1.9 cm³. The median maximum and tumor margin radiation doses were 24 and 12 Gy, respectively. The median follow-up periods for MR imaging and audiometry were 74 and 38 months, respectively. The overall tumor control rate was 97.5%. Actuarial 3-, 5-, and 8-year hearing preservation rates were 55, 43, and 34%, respectively. On multivariate analysis, better hearing ability (GR Class I) at the time of GKS and the mean cochlear dose (below 6 Gy) affected hearing preservation significantly.

Conclusions: GKS is an effective and reasonable alternative to resection, with satisfactory long-term tumor control for the patients with small VSs. Factors related to hearing preservation included a GR Class I hearing pre-GKS and a lower mean cochlear radiation dose. To retain serviceable hearing, it is important to apply GKS treatment while patients retain GR Class I hearing.

Perspective: It is hard to decide the treatment strategy for the patients harboring small-sized VSs who retained serviceable hearing. In the aspect of tumor control, there is little doubt that GKS is an excellent treatment tool for small-sized VSs. The problem is hearing deterioration after GKS. Many physicians choose the “wait and see” strategy in VS patients with serviceable hearing due to this problem. The authors report that better hearing function at the time of GKS and lower cochlear dose provide better hearing outcome after long-term follow-up of GKS. Although there is no statistical significance, they also report that smaller tumor volume could be a favorable prognostic factor for hearing preservation. Considering the long-term follow-up patients of this article were treated with older and perhaps outdated GKS techniques, the hearing results after modern GKS technique of small lesions might be better. Therefore, the data shown this article here support that early tumor detection (if possible), early GKS, and exquisite dose planning (adequate margin dose and decrease cochlear dose) could produce better results for the hearing-preserved VS patients in terms of hearing preservation as well as tumor control.

Summary written by: Jin Mo Cho, MD

Chang EL, Wefel JS, Hess KR, Allen PK, Lang FF, Kornguth DG, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: A randomized controlled trial. Lancet Oncol 2009;10:1037-44.

Study Question: Does the addition of whole-brain radiation therapy (WBRT) to stereotactic radiosurgery in the treatment of brain metastases worsen neurocognitive outcome?

Materials and Methods: The authors performed a prospective randomized trial on patients who presented with 1–3 brain metastases. Patients were randomized into SRS alone or SRS + WBRT arm. Patients were stratified by recursive partitioning analysis, number of brain metastases, and histology (radioresistance). The primary endpoint studied was neurocognitive function measured by the Hopkins Verbal Learning Test-Revised (HVLT-R).

Results: Fifty-eight patients were recruited. Thirty patients in the SRS alone arm and 28 patients in the SRS + WBRT arm were analyzed. Patients who received SRS + WBRT were found to have a mean posterior probability of decline of 52% at 4 months compared to the SRS alone group (mean posterior probability of decline of 24%). The authors also found that the SRS + WBRT group had a higher probability of delayed recall, recognition, and executive function compared to the SRS alone group. Interestingly, the overall survival between
the two groups showed a benefit in the SRS alone group. The study was stopped early by the monitoring committee because the committee found a clear benefit for SRS alone group.

**Conclusion:** The authors suggested that the addition of WBRT to SRS alone subjected the patient to a higher risk of neurocognitive deficits.

**Perspective:** The use of WBRT for the treatment of brain metastases is controversial. The benefits of WBRT are thought to control of local disease, control of distant sites, and minimal neurocognitive deficits. However, some feel that the there are significant neurocognitive deficits with WBRT and have argued that SRS alone provides minimal toxicity with excellent local control. Furthermore, the addition of salvage therapy with SRS has been shown to not compromise the overall survival of patients when compared to patients treated with WBRT.

Prior studies examined the addition of WBRT to SRS and concluded that there was no difference in neurocognitive outcomes with the addition of WBRT; however, most studies only used a cursory exam (mini-mental status exam) to assess neurocognition. The studies suggested that the decline in neurocognitive function is a result of the tumor burden in the brain. Chang *et al.* assessed the issue of neurocognition with more sophisticated tests to assess memory and executive function and found an increased risk for deterioration of neurocognition when WBRT was added to SRS. Furthermore, they found increased survival in patients who received SRS alone and suggested that this was due to less interruption of a patient’s chemotherapy regimen. While this study is still considered controversial, it gives evidence to considering the use of local therapy first when treating patients with oligometastases.

Summary written by: Michael Lim, MD

**Kappos L, Li D, Calabresi PA, O’Connor P, Bar-Or A, Barkhof F, et al. Ocrelizumab in relapsing-remitting multiple sclerosis: A phase 2, randomised, placebo-controlled, multicentre trial. Lancet 2011; 378:1779-87.**

**Study Question:** Does depleting the B cell population with antibody-mediated immune response improve MRI lesions in patients with relapsing remitting multiple sclerosis?

**Materials and Methods:** An international, randomized, double-blinded, and multicenter trial screened 273 patients with relapsing remitting multiple sclerosis for enrollment in this trial. Patients received either placebo or low-dose ocrelizumab (antibody targeting CD20 B cells) or high-dose ocrelizumab or interferon beta.

**Results:** Two hundred and twenty patients were eligible and enrolled in this trial, with half (110 patients) of them in ocrelizumab treatment arm. The total number of gadolinium-enhancing MRI lesions was decreased in the patients treated with ocrelizumab when compared to those in placebo or interferon beta groups. Although there were slightly fewer lesions in the high-dose ocrelizumab group compared to the lower dose treatment arm, the higher dose ocrelizumab group also had a slightly higher rate of serious adverse effects. This improvement in T1 gadolinium-enhancing MRI lesions was apparent by week 8 and this improvement also persisted till the end of the study period at 24 weeks.

**Conclusions:** B cell depletion with ocrelizumab appears to be effective in reducing the total number of T1 gadolinium-enhancing MRI lesions, which persists till 24 weeks. This improvement appears to correlate with disease activity and relapse improvement in these patients.

**Perspectives:** Relapsing remitting multiple sclerosis remains a difficult clinical therapeutic challenge. Utilizing ocrelizumab to target the humoral immune system for B cell depletion appears to be effective in reducing the overall number of T1 gadolinium-enhancing MRI lesions and relapsing disease activity. Although high-dose ocrelizumab group had a greater reduction in number, this group also had higher serious adverse reactions, including a death. Although there were no apparent effects of immunosuppression or opportunistic infection related morbidity, the duration of this study was short, which may have led to missing such activity. Lastly, this international multicenter, double-blinded, randomized study suggests that immune modulating therapies may play a greater role in disease mitigation as our understanding of various immune mechanisms continues to expand.

Summary written by: Isaac Yang, MD