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Key Words: C2 nerve root, hydrocephalus, lumbar spinal stenosis, pseudoprogression, vestibular schwannoma

EVALUATION OF PSEUDOPROGRESSION IN PATIENTS WITH GLIOBLASTOMA MULTIFORME USING DYNAMIC MAGNETIC RESONANCE IMAGING WITH FERUMOXYTOL CALLS RANO CRITERIA INTO QUESTION.[6]

Study Question: Study Question: Does the Response Assessment in Neuro-Oncology (RANO) criteria adequately evaluate for pseudoprogression following chemoradiation for the treatment of glioblastoma?

The authors of this study aim to evaluate the role of magnetic resonance imaging (MRI) with ferumoxytol in the diagnosis of pseudoprogression after treatment of glioblastoma. Current treatment standards include maximal safe surgical resection followed by concomitant temozolomide and conformal radiation. In general, the risk of posttreatment radiation necrosis is approximately 5–30% and presents typically between 3 and 18 months posttreatment. However, radiation necrosis has been reported decades after initial therapy. Currently, the RANO criteria is one of the most widely used criteria to assess treatment response within clinical trials. The criteria for true pseudoprogression require pathological confirmation or new lesions outside the radiation field within 12 weeks of treatment. Outside of these stipulations, pseudoprogression can only be classified as a possible diagnosis.

In an effort to better define pseudoprogression, the authors evaluated 56 glioblastoma patients with

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conventional MRI findings concerning for progression of disease. The authors used a 3 Tesla ferumoxytol-based perfusion MRI to assess relative cerebral blood volume measurements with areas concerning for progression normalized to normal appearing white matter. Based on prior data, a threshold of 1.75 was used as a cutoff for differentiating pseudoprogression from progressive disease. The authors identified 48% of patients with pseudoprogression. Of these patients with pseudoprogression, 30% displayed this finding greater than 3 months after the completion of treatment. Furthermore, overall survival was significantly longer (35.2 vs. 14.3 months, $P < 0.001$) in patients with pseudoprogression as compared with progressive disease.

The role of ferumoxytol-based MRI is a valuable tool in diagnosing pseudoprogression without biopsy. The authors effectively displayed the value of diagnosing this condition with regard to overall survival and demonstrated that pseudoprogression is frequent beyond 3 months.

Perspective: This study provides insight in to the current limitations of the RANO criteria. Consequently, radiographic worsening beyond 3 months does not indicate definitive tumor progression. Currently, the RANO criteria are the primary measure by which clinical trials are evaluated for tumor control versus progression. Dynamic MRI provides an additional diagnostic tool outside of open biopsy in delineating between pseudoprogression and tumor progression. Therefore, relative cerebral blood volume measurement through ferumoxytol MRI should be considered in the diagnosis of progression through the RANO criteria. Future prospective studies with larger cohorts will serve to further validate the results seen in this study.

Summary Written by: Johnathan H Sherman MD

C2 NERVE ROOT TRANSECTION DURING C1 LATERAL MASS SCREW FIXATION: DOES IT AFFECT FUNCTIONALITY AND QUALITY OF LIFE?[2]

Study Question: How does C2 nerve root transection during C1 lateral mass placement affect functionality and quality of life?

The authors conducted a 2-year prospective study on patients undergoing posterior atlantoaxial arthrodesis using the standard Harms and Melcher technique that involves the placement of C1 lateral mass polyaxial screws as well as either pars interarticularis, or pedicle screws at C2. Twenty-eight patients were enrolled in this study. Eight of these patients had their C2 nerve roots transected during C1 lateral mass screw placement, while in 20 patients the C2 nerve roots were preserved. A standard questionnaire was used to determine the presence, severity and frequency of occipital numbness/pain, and its effects on functionality and quality of life (QOL). In addition domains of the neck disability index (NDI) were used to quantify physical disability specific to occipital numbness. While there were trends towards lower estimated blood loss (338 vs. 235 ml), and lower length of surgery (167 vs. 153 min) favoring the nerve severing group, these did not achieve statistical significance. Regarding postoperative outcomes, occipital numbness was reported by 50% of patients following C2 transection, while occipital neuralgia was reported by 35% of patients with C2 preservation. None of the patients with numbness after C2 transection reported being "bothered" by it, while all patients with occipital neuralgia following C2 sparing reported being "bothered" by it and, 57.1% reported a moderate-to-severe effect on QOL. A total of 71.4% of patients with neuralgia reported the use of medications while none of the patients with numbness used any medications. Lastly, the mean disability was significantly higher with neuralgia compared to numbness ($P = 0.016$).

Perspective: The Harms and Melcher technique is the most commonly used method for posterior C1 and C2 stabilization that utilizes the placement of polyaxial screws into the C1 lateral masses. The entry point for C1 screw placement is usually in the middle of the lateral mass at the level of an unnamed emissary vein. In order to expose it, subperiosteal dissection is often conducted along the posterior arch of C1 and then deeper into the lateral mass. This is oftentimes tedious and obscured by bleeding from the vertebral venous plexus and by the presence of theC2 nerve root. Goel *et al.*[3] have pursued sectioning of the C2 nerve roots bilaterally proximal to the C2 ganglion, advocating that it enhances exposure, reduces bleeding, and allows for the opportunity for direct C1/C2 joint decortication, and hence arthrodesis. This study was the first prospective study to examine the effects of sacrificing the C2 root on the QOL and functionality in patients undergoing C1 lateral mass screw placement. While this study is limited by a small number of patients and the absence of preoperative and bassline outcome measures, it demonstrates the safety of C2 nerve root transection during these procedures. In fact, while C2 transection is associated with occipital numbness, this had no effect on QOL. On the other hand, C2 sparring was associated with occipital neuralgia that had negative effects on patient disability and QOL.

Summary Written by: Nader S. Dahdaleh MD

LONG-TERM QUALITY OF LIFE IN PATIENTS WITH VESTIBULAR SCHWANNOMA: AN INTERNATIONAL MULTICENTER CROSS-SECTIONAL STUDY COMPARING MICROSURGERY, STEREOTACTIC RADIOSURGERY, OBSERVATION, AND NONTUMOR CONTROLS.[1]

Study Question: How do microsurgery, stereotactic radiosurgery, and observation affect long-term quality of life in patients with small- to medium-size vestibular schwannomas?

The authors[1] conducted a cross-sectional study examining long-term health-related quality of life (HRQOL) in a large cohort of patients following observation, microsurgery, and stereotactic radiosurgery (SRS) for small- to medium-sized sporadic vestibular schwannomas (VSs) using three multipurpose HRQOL questionnaires and one recently validated disease-specific instrument. All patients with smaller than 3-cm sporadic VSs who underwent microsurgery, SRS or observation at one of two tertiary academic referral centers, one located in the United States and one in Western Europe, between 1998 and 2008 were surveyed via postal questionnaire using the 36-Item Short Form Health Survey (SF-36), the 10-item Patient-Reported Outcomes Measurement Information System short form (PROMIS-10), the Glasgow Benefit Inventory (GBI), and the Penn Acoustic Neuroma Quality-of-Life (PANQOL) scale. A total of 642 respondents were analyzed: 144 microsurgery, 247 SRS, and 148 observation patients in addition to 103 nontumor control patients. The mean interval between treatment and survey for patients with VS was 7.7 years. A multivariate regression model found no difference between management groups with respect to the PROMIS-10 physical or mental health dimensions, the SF-36 Physical or Mental Component Summary scores, or the PANQOL general, anxiety, hearing, or energy subdomains. SRS treatment or observation resulted in a better total PANQOL score and higher PANQOL facial, balance, and pain subdomain scores than the microsurgical cohort ($P < 0.02$). The nontumor control group and patients with VS had a greater difference in scores than the differences observed between individual treatment groups for the majority of measures.

Perspective: This study was the first multicenter study evaluating HRQOL in VS, includes the largest number of patients to date with the longest follow-up, compared HRQOL outcomes between all three management arms, and used three general HRQOL instruments and a recently validated disease-specific questionnaire that minimized the risk of monomethod bias. The authors found that the differences in HRQOL outcomes following SRS, observation, and microsurgery for VS are small, and the diagnosis of VS rather than the treatment strategy more significantly impacts QOL. Importantly, improvements in patient counseling regarding realistic long-term expectations of disease and offering psychosocial support may provide the most impact on HRQOL improvement. Given these findings together with the fact that many VSs remain stable in size following discovery, VSs less than 3-cm in size should be managed with observation initially, with intervention reserved for unequivocal growth or intractable symptoms that are amenable to treatment. The management of small- to medium-sized VS cannot be "one size fits all." A personalized management approach must be undertaken for each patient, taking into account tumor size and characteristics, patient age and health, symptoms, and patient preference.

Summary Written by: Isaac Yang, MD and Panayiotis Pelargos

ENDOSCOPIC THIRD VENTRICULOSTOMY AND CHOROID PLEXUS CAUTERIZATION IN INFANTS WITH HYDROCEPHALUS: A RETROSPECTIVE HYDROCEPHALUS CLINICAL RESEARCH NETWORK STUDY.[4]

Study Question: What are the outcomes of endoscopic third ventriculostomy and choroid plexus cauterization (ETV + CPC) for treatment of pediatric hydrocephalus in a North American population?

Children aged <2 years old in the Hydrocephalus Clinical Research Network multi-institutional registry who underwent ETV + CPC before November 2012 were included in the study. Outcomes and morbidity were retrospectively examined for ETV + CPC patients and for age-matched children who had first-time ventriculoperitoneal shunt placement for hydrocephalus. Included were 36 patients who underwent ETV + CPC, of which 13 patients had a history of previous shunt. These 36 ETV + CPC patients had the following hydrocephalus etiologies: Intraventricular hemorrhage of prematurity (9 patients), aqueductal stenosis (8), myelomeningocele (4), and other (15). Time to first treatment failure (requiring another surgery for hydrocephalus) was defined as the primary outcome. Fifty percent of the 36 ETV + CPC patients failed. Failure occurred at a median time of 30 days (4–484 days) after ETV + CPC surgery.

ETV + CPC success rates at 3-, 6-, and 12-months after surgery were 58%, 52%, and 52%, respectively. Using the validated ETV Success Score to calculate the predicted rate of success for the group, the expected success rate of ETV-only surgery for this cohort overall would be 50%. The authors note some limited evidence for improved outcome for patients who received ETV with near-complete (≥90%) choroid plexus cauterization,

suggesting that the effect of CPC may have a dose–response effect.

This early North American multicenter experience reports on 36 infants with ETV + CPC. Overall outcomes at 6 months are similar to ETV alone. Treatment in half of all patients failed, with median time to failure of 30 days. ETV + CPC is shown in this study to be a reasonably safe alternative to cerebrospinal fluid (CSF) shunt placement for infants with hydrocephalus. There was no independent adjudication of outcome, so there may be bias in the decisions regarding subsequent CSF diversion following the index surgery. The ages of the ETV + CPC and shunt patients were not quite comparable, with the ETV + CPC patients being older.

Perspective: The Hydrocephalus Clinical Research Network (HCRN) is a tightly controlled group representing highly specialized Pediatric Neurosurgery centers in North America. They present the retrospective experience of HCRN members with ETV + CPC in North America, and they report less optimistic outcomes than Dr. Benjamin Warf's experiences in East Africa. They report that the ETV + CPC surgery is safe, though they do report a higher failure rate than known CSF shunt placement failure rates. It remains to be seen how to weigh the chance at shunt freedom with ETV + CPC with its higher failure rate, given the known lifelong burden of CSF shunting. Neurocognitive outcomes and long-term outcomes are not well-characterized to date. What is the acceptable differential in outcomes for surgeons and patients, given the known downstream burden of CSF shunts and possible downstream sequelae of ETV + CPC? Many questions remain. A prospective ETC + CPC study is planned by the HCRN, which hopefully will further delineate the role of ETV + CPC in the treatment of pediatric hydrocephalus in North America.

Summary Written by: By Sandi Lam MD

INTERSPINOUS PROCESS DEVICES VERSUS STANDARD CONVENTIONAL DECOMPRESSION FOR LUMBAR SPINAL STENOSIS: COST-UTILITY ANALYSIS.[7]

Study Question: Is the use of an interspinous fixation clamp cost effective when compared with noninstrumented lumbar decompression?

The authors studied patients with intermittent neurogenic claudication, including patients aged 40–85 and with one or two level lumbar canal disease. This was a multi-center, double-blinded randomized trial. Over a 35-month period, 161 patients were enrolled and 159 analyzed. This included enrollment at five separate neurosurgical centers, including one academic and four secondary centers. Eighty patients were treated with an interspinous process device (IPD) and 79 had traditional lumbar decompression without instrumention. Outcome measures included quality-adjusted life years (QALYs), estimated societal cost per year (estimated from The Netherlands EuroQol 5D [EQ-5D) and EuroQol visual analog score, and diaries of cost). This was a registered trial in the Netherlands (Dutch Trial Register Number: NTR1307).

The results of this trail failed to show valuation in the use of an IPD device. According to the EQ-5D results, the valuation of life after implantation of the IPD versus standard decompression was not different. Mean utilities were less favorable after the IPD according to EQ-5D with a difference in QALY of 0.024 (confidence interval [CI]: -0.031 to 0.079). Overall, the cost of IPD placement was higher with an increase of 3030 Euro per patient (95% CI: 561–5498 Euro). This was primarily from implant cost (2350 Euro per implant). As a result, from a societal perspective, there was a 2762 Euro difference in favor of traditional bony decompression.

Perspective: Lumbar spinal decompression for intermittent neurogenic claudication is an extremely effective and durable procedure in patients with progressive symptoms that fail to respond to conservative care. To improve upon this procedure, any new technique must be both more effective and equally safe. Furthermore, the additional placement of spinal instrumention (and its resultant extra cost) must be carefully evaluated. This is especially important in our current health-care environment where procedural and societal costs from surgical procedures are under intense scrutiny.

The efficacy of IPDs has not yet been well established.[8] They have not been shown to improve outcomes when compared with traditional lumbar decompression.[5] Furthermore, in patients without spinal instability, such as in the current study, one must question the biomechanical or clinical benefit of adding these devices in an already effective and established surgery. Although we acknowledge the ultimate goal of improving our day-to-day techniques, the significant added cost of these devices requires a matching clinical benefit.

Summary Written by: Zachary A. Smith, M.D.

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