Is Re-Irradiation of Recurrent Metastatic Brain Tumors an Option?

Re-Irradiation for Metastatic Brain Tumors With Whole-Brain Radiotherapy.

Akiba T, Kunieda E, et al:

Jpn J Clin Oncol 2012; 42 (April): 264-269

Retreatment with whole-brain radiation therapy may be an option for patients with relapse or recurrence of brain metastases.

Background: Relapse after whole-brain radiation therapy (WBRT) for multiple cerebral metastases occurs fairly often and is associated with a poor prognosis. Re-irradiation is an option that many defer because of risks of exceeding brain tolerance and resulting toxicity.
Objective: To determine if brain re-irradiation is beneficial.
Design: Single-institution retrospective study.
Methods: Patients with ≥2 courses of WBRT for relapse or recurrence of metastatic brain tumor between 1994 and 2009 were included. Treatment usually consisted of lateral opposing fields with 6 to 18 MV photon beams 5 days a week. Data reviewed included primary cancer location, patient age and gender, Karnofsky performance status (KPS), radiation doses and fractionation, intervals between irradiation treatments, symptomatic responses, tumor response evaluated by MRI, adverse effects using the Late Radiation Morbidity Scoring Schema, and survival.
Results: Of 585 cancer patients treated with WBRT, 31 (26 with lung primary and 5 with breast primary) had at least a second course of WBRT. Mean age at re-irradiation was 56 years; 84% of patients had active extra-cranial disease at the time of retreatment. Initial WBRT was to 30 Gy in 10 fractions for 87%. Repeat WBRT was to 30 Gy in 10 fractions in 42% of patients. Ninety-seven percent of patients had chemotherapy, including 29% with molecular-target agents. The median interval between initial WBRT and re-irradiation was 10 months. The median survival after initial cancer diagnosis was 26 months, and median survival after re-irradiation was 4 months; 65% of patients had symptomatic improvement after re-irradiation, with partial or complete tumor response of 55%. Fifty-two percent of patients had Grade 1 acute radiation reactions, including headache (29%) and nausea (26%); 23% had subacute otitis media. Of the patients studied, 36% had MRI evidence of brain atrophy after initial WBRT, and 74% did so after re-irradiation; 32% had Grade 2 or higher cognitive disturbance or encephalopathy at a median of 3 months after repeat WBRT. Of the 11 patients who died of neurogenic causes, 9 had carcinomatous meningitis. Factors associated with longer survival included lung primary and a KPS score of ≥70 at the time of re-irradiation.
Conclusions: Whole-brain re-irradiation showed promising effectiveness with only a slight burden on patients in the acute phase.
Reviewer's Comments: Relapse with multiple cerebral metastases after WBRT is difficult to treat. This study shows some additional survival with relatively mild adverse side effects. The authors point out several limitations in their small series -- no detailed neuro-cognitive evaluation, no objective evaluation of neurological impairments, and no determination that survival or symptom improvement was related to re-irradiation. Most significantly, which patients were appropriate for re-irradiation was also not defined. A comparison of the survival and symptoms of those who underwent re-irradiation compared to those who did not, despite relapse, would have been helpful. At this point, I would consider re-irradiation with WBRT in carefully selected patients. (Reviewer-N. Scott Litofsky, MD).

Keywords: Brain Metastases, Re-Irradiation, Whole-Brain Irradiation

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Caregivers of Brain Tumor Patients Have Diminished Quality of Life

The Burden of Brain Tumor: A Single-Institution Study on Psychological Patterns in Caregivers.

Finocchiaro CY, Petruzzi A, et al:

J Neurooncol 2012; 107 (March): 175-181

Despite a negative impact on their quality of life, caregivers of brain tumor patients have increased self esteem, deservedly so.

Background: While it is intuitive that caregivers of brain tumor patients experience a reduced quality of life, it is nonetheless important to try to characterize and quantify this impact in order to devise interventions.
Objective: The authors of this paper report the insights they gained by studying this issue.
Methods: The cohort consisted of 100 caregivers of brain tumor patients treated through the Neuro-oncology Department of the IRCCS Instituto Neurologico Carlo Besta in Milan, Italy. Demographic characteristics of the participants were collected. Caregivers then completed the short form-36 (SF-36), the Hospital Anxiety and Depression Scale, and the Caregiver Reaction Assessment Scale. Appropriate statistical tests were used to document clinical significance.
Results: The mean age of the 100 caregivers was 50 years. Of these, one-third were male and two thirds were female. Two thirds of caregivers were a spouse or partner. Of the patients, 75% had a high-grade CNS malignancy. In regard to the SF-36 survey, the caregivers' responses were compared to a sample of >2000 healthy adult Italians. The caregivers scored significantly lower in vitality, social functioning, and emotional functioning compared to the control group. In regard to the Hospital Anxiety and Depression Scale, the caregivers' responses were compared to nearly 2000 adults from the United Kingdom. The caregiver group experienced a statistically significant increase in anxiety and depression compared to the control population. In regard to the Caregiver Reaction Assessment Scale, the caregivers' responses were compared to those of a population of "informal" caregivers of brain tumor patients. The study group of caregivers had higher scores for self esteem, experienced a greater financial impact, and felt they had decreased family support compared to the control population. The patients' tumor grade did not have an impact on the psychological health of the caregivers. Anxiety was higher in caregivers of patients with lower Karnofsky performance scores. Female caregivers experienced a greater mental health impact than their male counterparts, regardless of tumor grade. Women caregivers also perceived a greater lack of support than did men. Older caregivers experienced a greater quality of life impact than did younger caregivers.
Conclusions: Caregivers of brain tumor patients have a clinically significant decrease in their quality of life.
Reviewer's Comments: This study confirms what we would have expected: caregivers of brain tumor patients experience anxiety and depression, worry about finances, perceive a lack of support, and, in general, have a diminished quality of life. A surprising finding, at least to me, was the higher level of self esteem experienced by caregivers. The reason this article is important is that it brings this seldom-discussed issue to light. I find that preparing patients and their caregivers for the quality-of-life issues they will face is immensely helpful and much appreciated. (Reviewer-Richard Rovin, MD).

Keywords: Caregiver, Quality of Life, Brain Tumor

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Failed SRS Increases Subsequent Surgical Risk in Patients With VSs

Surgical Treatment of Patients With Vestibular Schwannomas After Failed Previous Radiosurgery.

Gerganov VM, Giordano M, et al:

J Neurosurg 2012; 116 (April): 713-720

Surgery after previous partial tumor removal and radiosurgery is related to worse outcome in patients with vestibular schwannomas.

Background: As the treatment of vestibular schwannomas (VSs) has become commonly performed with stereotactic radiosurgery (SRS), increasing numbers of patients have experienced treatment failure.
Objective: To assess the risk of surgical treatment after SRS treatment failure.
Methods: The authors used 3 groups of patients in their analysis. Group A included patients initially treated with SRS. Group B included patients initially treated with subtotal surgical resection followed by SRS. Patients in these groups all failed SRS with subsequent sustained tumor growth and/or development of neurological symptoms and required surgical resection. Twenty-eight patients were included in these 2 groups. They were compared to 30 patients treated with surgical resection alone without previous SRS.
Results: Gross total resection was achieved in nearly all patients (>96%). Rates of new cranial neuropathies and cerebrospinal fluid (CSF) leakage were highest in group B patients. Patients in both groups A and B had higher rates of postoperative hematoma formation. Facial nerve preservation rates were much lower in group B patients (61.5%) than in group A patients (86.7%) and in patients in the control group (93.3%).
Conclusions: Failed SRS increases subsequent surgical risk, particularly in cases of previous subtotal resection.
Reviewer's Comments: This article highlights an increasingly difficult conundrum in the management of VSs. As more tumors come to the attention of treating physicians after failed radiosurgery, it has become increasingly apparent that surgical resection is more hazardous than when performed in the absence of prior radiosurgery. The authors' finding of worsened outcome in their group B patients is of particular interest. There has clearly been a paradigm shift in the management of larger VSs in the radiosurgical era toward planned subtotal resection followed by SRS. The findings of the authors mirror our own that, in fact, secondary surgery after initial failure of SRS to control residual tumor is particularly hazardous and is associated with significant morbidity. For these and other reasons, we continue to advocate for the management of large VSs in large tertiary care centers with significant experience in surgical resection of these tumors. We also advocate a philosophy of attempted gross total resection in most cases, reserving subtotal resection for older patients or those in whom intraoperative findings dictate a more conservative approach. (Reviewer-Nicholas C. Bambakidis, MD).

Keywords: Facial Nerve, Radiosurgery, Vestibular Schwannoma

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Chemotherapy Is Option for Malignant Pituitary Tumors

Pituitary Carcinomas and Aggressive Pituitary Tumours: Merits and Pitfalls of Temozolomide Treatment.

Raverot G, Castinetti F, et al:

Clin Endocrinol 2012; 76 (June): 769-775

Early data suggest that malignant pituitary tumors in patients with malignant pituitary tumors respond to temozolomide.

Background: Pituitary adenomas with malignant behavior and pituitary carcinomas are notorious for their resistance to chemotherapeutic agents. We will review the data from the past few years showing a response to temozolomide (TMZ). To this day, only case reports have been published.
Objective: To review recent advances in the treatment of malignant pituitary tumor.
Design: Retrospective study.
Methods: Critical review of the current knowledge.
Results: Malignant pituitary tumors include atypical adenoma (defined by a mitosis fraction >3% and expression of the p53 suppressor gene), invasive adenoma, and carcinomas. After resection, these tumors recur; they are often radioresistant and grow rapidly. Just as with regular pituitary adenomas, these tumors can be hormone secreting or non-functional. They metastasize to the brain, spinal cord, and sometimes to the lymph nodes, lungs, liver, and bones. TMZ has recently been used to treat these tumors, leading to tumor control in 50%, as objectified by decreased hormonal secretion and/or decreased tumor volume. Response rates are possibly better in ACTH and prolactin secreting tumors. The response to TMZ would also depend on the degree of expression of the DNA repair enzyme MGMT. When tumor cells have a high MGMT activity, the DNA damage induced by TMZ is repaired, which, in essence, negates its effect. Accordingly, malignant pituitary tumors with a low immunostaining for MGMT have an increased response to TMZ. This needs to be confirmed by a proper clinical trial. The current clinical data show an initial response to a standard regimen of TMZ (200 mg/m2 for 5 days every 28 days), but that response fades away after 5 to 8 months.
Conclusions: Clinical trials will provide a better indication on the right candidate for TMZ and what the optimal dose regimen will be.
Reviewer's Comments: These results are encouraging; 60% of malignant pituitary tumors respond to TMZ and even more if they are prolactin or ACTH secreting. Because <50 patients treated with TMZ have been reported and because this pathology is rare, close collaboration between institutions treating these patients and a proper clinical trial are needed. Meanwhile, patients with a recurrent aggressive pituitary tumor after surgery and radiotherapy should be offered TMZ regardless of whether their tumor is immunopositive for MGMT, Future therapies might include agents that will silence the expression of MGMT, allowing a better response to TMZ. (Reviewer-Luc Jasmin, MD).

Keywords: Pituitary Atypical Adenoma, Carcinoma, Temozolomide, MGMT, Ki-67, p53

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Check for Contrast Enhancement for Cerebral Contusions

Early Parenchymal Contrast Extravasation Predicts Subsequent Hemorrhage Progression, Clinical Deterioration, and Need for Surgery in Patients With Traumatic Cerebral Contusion.

Huang AP-H, Lee C-W, et al:

J Trauma 2011; 71 (December): 1593-1599

Contrast enhancement on CT after cerebral contusion may predict hemorrhage volume increase.

Background: Hemorrhage progression after traumatic cerebral contusion commonly occurs and may be associated with neurological decline and/or the need for surgery. No single clinical parameter accurately predicts contusion progression.
Objective: To evaluate the predictive potential of parenchymal contrast enhancement for subsequent contusion progression.
Design: Single-institution prospective case series.
Methods: Patients aged 16 to 75 years with cerebral contusion on initial contrast-enhanced and perfusion computed tomography (CEPCT) scans within 6 hours of traumatic brain injury (TBI) were evaluated. CT angiography (CTA) and CEPCT were analyzed for parenchymal contrast extravasation and spot sign (a bright spot on source CTA images predictive of hemorrhage progression). Follow-up CT 24 and 72 hours later was analyzed for hemorrhage progression, defined as >30% or a 5 mL increase in hemorrhage volume (VH). Patients were excluded if they were pregnant, were coagulopathic (prothrombin time >12.2 seconds, partial thromboplastin time >35.5 seconds, or platelet count <100,000/mL), were on antiplatelet or anti-coagulant medication, had poor renal function (creatinine >1.4 mg/dL or creatinine clearance rate <45 mL/min), had penetrating injury, had a brain stem injury, had hemodynamic instability, had systolic blood pressure <90 mm Hg, or required emergency surgery.
Results: During the 20-month study period, 22 of 226 patients were included, with mean age of 59.4 years and an average initial Glasgow Coma Scale score of 12.9 (range, 9 to 15); 86% of patients had subarachnoid or subdural hemorrhage in addition to contusion, without a relationship to progression. Mean VH was 6 mL (range, 0 to 18 mL) and mean edema volume (VE) was 10 mL. Clinical neurological deterioration occurred in 8 of 22 patients (36%), 6 from hemorrhage progression and 2 from edema. Six patients (27%) required surgery. None of 22 patients had a spot sign; 9 of 22 (40.9%) had contrast enhancement (CE), which was associated with hemorrhage progression, clinical deterioration, and need for surgery, but not poor outcome. CE was associated with greater VE differences at 24 and 72 hours, but not greater VH differences. The positive predictive values of CE for progression, deterioration, and surgery were 66.7%, 77.8%, and 66.7%, and the negative predictive values were 84.6%, 92.3%, and 100%, respectively.
Conclusions: CE is associated with hemorrhage expansion, clinical deterioration, and the need for surgery in patients with traumatic cerebral contusion.
Reviewer's Comments: This interesting study shows that contrast enhancement on initial CT after traumatic cerebral contusion can predict an increase in contusion size and clinical neurological deterioration. The authors did not define their indications for surgery, so the predictive value for CE for surgery is limited. Of note, only 10% of patients with cerebral contusion were eligible for this study, which further limits the predictive value of the CEPCT. Further study is warranted; I will await these results before requesting this study for evaluation of my TBI patients. (Reviewer-N. Scott Litofsky, MD).

Keywords: Head Trauma, Contrast Extravasation, Perfusion, CT, Contusion, Blood-Brain Barrier

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Temporal Lobe Surgery in Children Is Efficient, Safe

Epilepsy Surgery of the Temporal Lobe in Pediatric Population: A Retrospective Analysis.

Lopez-Gonzalez MA, Gonzalez-Martinez JA, et al:

Neurosurgery 2012; 70 (March): 684-692

Approximately 50% of pediatric patients undergoing temporal lobe surgery for intractable epilepsy remain seizure free after 5 to 12 years after surgery.

Background: 20% to 25% of patients of all ages have intractable epilepsy, and, in the pediatric population, only 20% of patients have epilepsy of a temporal lobe origin. Temporal lobe surgery in selected patients is one of the most effective means to obtain seizure control with a reported seizure freedom after temporal lobectomy ranging from 60% to 86%. Early surgical intervention is also known to reduce the development of morbidity of epilepsy and anti-epileptic drugs (AEDs).
Objective: To further understand the role of temporal lobe surgery in pediatric patients with epilepsy.
Design/Methods: This was a retrospective analysis of 130 selected patients who underwent a temporal lobectomy between 1996 and 2006.
Results: The mean age at surgery was 12.3 years. Seizure frequency was daily in 28%, persistent in 68%, and rare in 4%. Invasive evaluations to localize seizure onset were required in 32 patients (24.5%), and a Wada test was used in 74 patients (56.4%). Intraoperative electrocorticography was performed in 20 patients (15.2%). The mean length of hospital stay for patients not requiring invasive evaluations was 5 days (range, 3 to 15 days) versus 12 days for those who required it. Hippocampal sclerosis was present in 70 patients (54%), 7 of whom had normal MRIs. Five patients (25%) had cortical dysplasia, and 3 (15%) had chronic inflammation and gliosis. Seizure freedom rates at 1, 2, 5, and 12 years were 76%, 72%, 54%, and 41%, respectively; 98 patients (75.3%) were class I, 11 (8.5%) were class II, 9 (7%) were class III, and 12 (9.2%) were class IV at last follow-up. Overall, seizures recurred in 54 patients (41%), and seizure control was re-obtained in 27 patients (50%) with adjustments of anticonvulsant therapy. Complications were present in 9 patients (7%). Anticonvulsant therapy was successfully discontinued in 36 patients (28.3%) after a mean period of 18 months.
Conclusions: Temporal lobectomy is efficient and safe.
Reviewer's Comments: Important aspects of the article for counseling are as follows: (1) having a normal MRI does not reduce the chances of being seizure free compared to patients with an evident pathology; (2) in the first 10 years after surgery, expect an increase in the frequency of seizure despite having achieved seizure freedom, but up to half of patients will return to a good seizure control with AED adjustment; and (3) only about one third of patients manage to be weaned completely from the AEDs. Other useful information to use is the 7% complication rate, which is similar to that of previous publications, and the 10% postsurgical depression rate. Finally, probably the most encouraging information is that, long term, up to 84% of patients achieve an Engle class II seizure control outcome. (Reviewer-Amir Kershenovich, MD).

Keywords: Surgery, Intractable Epilepsy, Children

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More Rest Doesn't Mean Fewer Complications

Increased Rate of Complications on a Neurological Surgery Service After Implementation of the Accreditation Council for Graduate Medical Education Work-Hour Restriction.

Dumont TM, Rughani AI, et al:

J Neurosurg 2012; 116 (March): 483-486

Resident work-hour restrictions may lead to an increase in patient complications.

Background: The Accreditation Council for Graduate Medical Education (ACGME) mandated work-hour restrictions for residents in training in 2003, in part to improve patient safety. Several studies have shown reduced scholarship and test scores after work-hour restriction initiation; patient safety measurement has been more difficult.
Objective: To compare morbidity and mortality before and after ACGME-mandated work-hour restrictions.
Design: Single-institution retrospective case series using a prospective database.
Methods: Patient complications (death [mortality] and non-death [morbidity]) were entered into a database by residents and the attending neurosurgery team. These complications were characterized as avoidable (preventable or possibly preventable) or unavoidable. Morbidity and mortality rates were determined for 3 time periods: July 2000 to June 2003 (pre-restriction); July 2003 to June 2006 (post-restriction 1); and July 2006 to June 2009 (post-restriction 2).
Results: 12,957 patients were admitted over the 9 years of the study. Diagnoses were similar between time periods, except post-restriction 1 had more patients with atraumatic subarachnoid hemorrhage and peripheral nerve surgery and fewer patients with neurotrauma. Morbidity (89 per 1000 patients) was slightly higher, and mortality (27 per 1000 patients) was slightly lower in post-restriction 1 relative to pre-restriction (70 per 1000 and 32 per 1000, respectively), but not significantly so. Avoidable morbidity significantly increased in post-restriction 1 (56 to 66 per 1000 patients). In secondary analysis, post-restriction 2 morbidity (91 per 1000 patients) and mortality (33 per 1000) were significantly higher than either of the previous time-periods. Post-restriction 2 patients were more likely to have atraumatic subarachnoid hemorrhage, neurotrauma, and peripheral nerve surgery, but were less likely to have spinal surgery than in other time periods.
Conclusions: Morbidity rates increased after implementation of ACGME-mandated work-hour restrictions on an academic neurological surgery service.
Reviewer's Comments: ACGME mandated work-hour restrictions have created significant angst for training programs and residents, particularly in neurological surgery. Concerns have been raised about the overall quality of training in a specialty requiring increasing knowledge and skill sets with reduced time to master those essential components. In this study, patient morbidity (and mortality, if one considers the latest time period) is increased after work-hour restriction implementation. In fact, the latest epoch had the greatest complication rate, suggesting some continued deterioration in patient safety as adaptation of restrictions became more entrenched. While these parameters are rather crude measures of patient safety, this study illustrates that the hoped for result of these mandates was not realized. This study does not address the reasons why complication rates increased after work-hour restrictions were instituted. Increased care-handoffs may contribute; overall resident experience may be another factor, as may other unrelated non-resident issues. These results, however, should concern all neurosurgeons and policy makers. Perhaps senior neurosurgeons may be asked to mentor their junior colleagues in practice more often. Further evaluation of any work-hour restriction mandates is essential to make sure unintended negative consequences do not occur. (Reviewer-N. Scott Litofsky, MD).

Keywords: Complications, Work-Hour Restriction, ACGME, Neurosurgery

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High Success Rate After Odontoid Screw Fusion

Analysis of Risk Factors Associated With Fusion Failure After Anterior Odontoid Screw Fixation.

Cho D-C, Sung J-K:

Spine 2012; 37 (January): 30-34

A fracture gap and delaying surgery increases the risk of non-union after odontoid screw fixation.

Background: Odontoid type II fractures can be treated either with a single trans-odontoid screw or by posterior C1-C2 fixation.
Objective: Drs Cho and Sung present their experience placing an odontoid screw as a first approach. They reviewed the results of 41 patients (33 men, 8 women) aged 46.6 ± 19.6 years (range, 15 to 79 years).
Design: Retrospective study from January 2002 to December 2007.
Methods: All procedures were performed by a single surgeon. Patients had a type II or shallow type III odontoid fracture (Anderson and D'Alonzo classification) with an intact transverse ligament, and all fractures were repaired with a single 4 or 4.5 mm trans-odontoid screw. The mean delay from injury to surgery was 9.39 days (range, 1 to 60 days). The follow-up was 14.7 ± 9.4 years and included 3-D scan.
Results: Bony union occurred in 80% of patients. Complete non-union was found in 13%, and all these patients underwent posterior C1-C2 fusion. Fibrous union of the odontoid occurred in 7% and was determined to be stable in all of these patients. The only surgery-related complication was a C1-C2 posterior screw pull-out. Regression analysis indicated that the risk of non-union increased by 37.5-fold when waiting more than a week to fuse, and by 21-fold when a gap of ≥2 mm was present at the fracture site. A horizontal displacement ≥2 mm did not increase the risk of non-union. Patients aged ≥60 years did not have an increased risk of non-union.
Conclusions: Odontoid screw fusion is effective for all ages if performed in the first 7 days, as long the fracture gap is <2 mm.
Reviewer's Comments: Some surgeons will offer a posterior fusion, and others are adamant that a trans-odontoid screw should be placed. Bringing the odontoid down with a lag screw regardless of the gap ≥2 mm might not be sufficient. In a recent retrospective study of 97 patients, Rizvi (*J Trauma* 2012: 73) showed a higher percentage of bony fusion with posterior instrumentation and when fractures were not displaced horizontally. This last point is in contrast to the present study. Posterior fixation has a few downsides, such as greater postoperative pain, greater neck stiffness, and reduced neck mobility. Given that most individuals with odontoid fracture are aged ≥60 years, the results of this study might not be applicable to many patients. Omeis (*J Spinal Disord* Tech 2009: 22: 91-95) found that, in patients aged ≥70 years, stability on flexion-extension was obtained in 56% after use of an odontoid screw and 69% after posterior fusion. Finally, the risk of instability after fibrous union is probably greater than suggested here according to Kirankumar and colleagues *(Neurosurg* 2005: 56: 1004-1012). (Reviewer-Luc Jasmin, MD).

Keywords: Odontoid Fracture, Trauma, Surgery, Outcome, Fusion Rate

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Efficacy of Diagnosing Open Spina Bifida at 11 to 13 Weeks' Gestation

Retrospective Review of Diagnostic Performance of Intracranial Translucency in Detection of Open Spina Bifida at the 11-13-Week Scan.

Fong KW, Toi A, et al:

Ultrasound Obstet Gynecol 2011; 38 (): 630-634

The presence of intracranial translucency excludes the diagnosis of open spina bifida at 11 to 13 weeks' gestation.

Objective: To determine the efficacy of intracranial markers for detecting open spina bifida at the 11- to 13-week ultrasound.
Design: This was a retrospective review done over a 4-year period.
Methods: During this time, a database of fetuses with known pregnancy outcomes was evaluated. All had had an 11- to 13-week nuchal translucency sonographic evaluation that was part of the aneuploidy screening. Sagittal images obtained for nuchal translucency measurements were evaluated by 2 independent observers. On a sagittal view, the fourth ventricle was seen as an intracranial translucency (IT) between the brain stem and the choroid plexus. In fetuses with open spina bifida, the fourth ventricle or IT was not seen. The observers were not aware of pregnancy outcomes. Each assessed the image for the presence of the brain stem, fourth ventricle, choroid plexus, and the cisterna magna. The images were evaluated according to the ability to see the IT, the overall adequacy of the IT image, and the reason for the inability to see the IT.
Results: There were a total of 191 normal fetuses and 8 fetuses with open spina bifida. The IT was seen in 150 of the 199 fetuses (75%); all of these fetuses were normal. In 6 of the 49 fetuses in which the IT was not seen, this was thought to be secondary to open spina bifida; however, 4 fetuses had open spina bifida, and 2 were normal. In the 43 cases, the inability to visualize the IT was thought to be secondary to inadequate image. Of these, however, 4 fetuses had spina bifida, but 39 were normal. The sensitivity, therefore, was 50%, and the specificity was 99%. Of the 191 normal fetuses, the IT was seen in 150 cases (79%) and was not seen in 41 cases (21%). The IT was more likely to be seen in the supine position when the fetal supine position was evaluated rather than the prone position. There was a 79% concordance between the 2 observers in evaluating the IT. One observer had a sensitivity of 88% and a specificity of 91%, whereas the second observer had a sensitivity of 0% but a specificity of 97%.
Conclusions: The intra-observer agreement for assessing IT at an 11- to 13-week ultrasound is moderate; open spina bifida could be excluded if the IT was well visualized.
Reviewer's Comments: It is interesting that, if the IT is seen, an open spina bifida appears to be reliably excluded; however, non-visualization of the IT appears more likely to be due to technical components more so than fetal abnormalities. It appears that further training regarding the identification of the IT is needed before this technique can be widely undertaken. (Reviewer-Thomas N. Tabb, MD).

Keywords: Intracranial Translucency, Open Spina Bifida, First Trimester, Ultrasonography

Print Tag: Refer to original journal article

Complications After CCSVI Procedures for MS May Be Significant

Complications in MS Patients After CCSVI Procedures Abroad (Calgary, AB).

Burton JM, Alikhani K, et al:

Can J Neurol Sci 2011; 38 (September): 741-746

Rigorous studies using multiple imaging modalities have not detected an association between multiple sclerosis and anomalous or pathological venous flow.

Background: The theory of chronic cerebrospinal venous insufficiency (CCSVI) has gained increasing attention over the past 1 to 2 years as a potential cause of multiple sclerosis (MS). This theory hypothesizes that MS patients have abnormal venous hemodynamics affecting the brain and spinal cord, caused by structural abnormalities of the azygous and internal jugular veins. Venous distention may then cause iron-laden erythrocytes to leak into surrounding tissues, provoking a secondary inflammatory cascade in the CNS. Rigorous studies using multiple imaging modalities have not detected an association between MS and anomalous or pathological venous flow. Nevertheless, a considerable number of MS patients have undergone endovascular CCSVI procedures, usually angioplasty and/or stent placement in the azygous or internal jugular veins, the safety of which are unknown.
Objective: To report on some of the complications in Canadian MS patients after undergoing CCSVI procedures abroad.
Design: Case series.
Participants: Subjects included 5 Canadian patients with confirmed MS who experienced complications after venous stenting and/or angioplasty procedures performed for presumed CCSVI outside of Canada (in Eastern Europe, India and the United States).
Methods: The charts of all subjects were reviewed.
Results: Complications included internal jugular vein stent thrombosis, cerebral sinus thrombosis, stent migration to a renal vein, cranial nerve (CN) injury (right CN XI and XII, and left CN XI), and injury associated with venous catheterization resulting in a retroperitoneal hematoma. One patient underwent stent placement in an azygous vein in Eastern Europe, although he did not provide consent for stent placement. Post-procedure treatment was with various platelet anti-aggregates or anti-coagulation for variable periods of time. Patient follow-up by the individuals performing these procedures was typically poor in these cases.
Conclusions: Complications and risks associated with venous stenting and angioplasty of jugular and azygous veins can be significant. As more MS patients seek these unproven procedures, often performed in foreign locations with poor follow-up, an increasing number of complications may be recognized.
Reviewer's Comments: The MS Society of Canada awarded grants for 7 observational studies in Canada and the United States in 2010 to determine the validity of the CCSVI hypothesis and to further characterize the nature of venous anatomy in MS patients. A registry to follow patients who have sought out the CCSVI therapy outside of Canada is planned in Alberta. This should provide more detailed information regarding how commonly complications of these procedures occur. Meanwhile, MS patients should be cautioned about potential complications associated with CCSVI interventional procedures. (Reviewer-W. Steven Metzer, MD).

Keywords: Complications, Etiology, MS, Venous Insufficiency; Treatment

Print Tag: Refer to original journal article

Catheter-Directed Thrombolysis Prevents PTS in Iliofemoral DVT

Long-Term Outcome After Additional Catheter-Directed Thrombolysis Versus Standard Treatment for Acute Iliofemoral Deep Vein Thrombosis (The Cavent Study): A Randomised Controlled Trial.

Enden T, Haig Y, et al:

Lancet 2012; 379 (January 7): 31-38

Catheter-directed thrombolysis should be considered in addition to conventional therapy in patients with iliofemoral deep venous thrombosis and low bleeding risk to reduce the incidence of post-thrombotic syndrome.

Background: Post-thrombotic syndrome (PTS) is characterized by chronic extremity pain/swelling after an acute deep venous thrombosis (DVT) fails to resolve.
Objective: To determine the effect of catheter-directed thrombolysis (CDT) in conjunction with conventional systemic anticoagulation and compression stockings to prevent PTS in persons with acute iliofemoral DVT.
Design/Methods: This was a prospective, multicenter, randomized controlled trial of 209 adults with first-time acute DVT of femoral, iliac, or combined veins. Exclusion criteria included symptoms >3 weeks before randomization, trauma/surgery within prior 2 weeks, current anticoagulant therapy, contraindications to thrombolytic treatment, hemoglobin <8 g/dL, platelet count <80,000/µL, creatinine clearance <30 mL/minute, systolic blood pressure >160 mm Hg, diastolic blood pressure >100 mm Hg, history of subarachnoid/intracerebral hemorrhage, any disease with <24-month life expectancy, or malignant disease with planned chemotherapy. Participants were randomized to conventional therapy comprised of initial treatment with low-molecular-weight heparin (LMWH) and warfarin followed by warfarin alone with a target international normalized ratio of 2.0 to 3.0 or to CDT in addition to conventional therapy. In the CDT group, LMWH was stopped 8 hours prior to venous catheter insertion across the thrombus. Alteplase, a recombinant tissue plasminogen activator, was infused into the catheter for ≤96 hours based on thrombus resolution. Continuous systemic unfractionated heparin was given simultaneously to keep the active partial thromboplastin time 1.2 to 1.7 times the upper limit of normal. Use of adjuvant venoplasty and/or venous stents was allowed at the clinician's discretion. LMWH was restarted with initiation of warfarin 1 hour after discontinuation of alteplase and unfractionated heparin. All patients in both groups were advised to use knee-high class II (30 mm Hg) compression stockings every day for 24 months.
Results: Iliofemoral patency on ultrasound at 6 months was higher with CDT plus conventional therapy compared to conventional therapy alone (65.9% vs 47.4%). At 24 months, the combination of CDT with conventional therapy led to a 14.5% reduction in PTS (41.1% CDT vs 55.6% controls) by Villalta scores. Drawbacks to CDT included acute bleeding complications (22% CDT vs 0% controls); 9% of these were clinically relevant (eg, abdominal wall hematoma, calf compartment syndrome). Overall, 4% of CDT participants had non-bleeding complications (eg, transient peripheral neurologic deficits, venipuncture site infection).
Conclusions: CDT for high proximal lower extremity DVT should be considered in patients with low bleeding risk to reduce incidence of PTS.
Reviewer's Comments: For the select patient with a high proximal lower extremity DVT, low bleeding risk, and high baseline function, I will consider referral for CDT. In these carefully selected patients, long-term potential benefit of PTS reduction likely outweighs the not insignificant risk of acute complications. (Reviewer-Melissa "Moe" Hagman, MD, FACP).

Keywords: Post-Thrombotic Syndrome, Deep Venous Thrombosis

Print Tag: Refer to original journal article

Similar Gene Mutations Found in Coronal and Metopic Craniosynostosis

Differential Expression of Extracellular Matrix-Mediated Pathways in Single-Suture Craniosynostosis.

Stamper BD, Park SS, et al:

PLoS One 2011; 6 (October 19): Epub ahead of print

Non-syndromic single-suture craniosynostosis patients demonstrate genetic mutations that may cause synostosis.

Background: Craniosynostosis is a pathological premature cranial suture closure. Increased intracranial pressure may result. The incidence is 1 per 2500 live births. The cause of disease is still unknown except for a few (7% to 10%) gene abnormalities in syndromic synostosis. Involvement for a single suture is 85% to 95% versus 5% to 15% for multiple sutures. Fifty percent of single-suture craniosynostosis involves the sagittal suture, 22% involves the coronal, 15% involves the metopic, and only 2% involves the lambdoid. Genetic mutations in single-suture craniosynostosis remain unknown.
Objective: To analyze transcriptomic data and to review genetic mutations in single-suture craniosynostosis.
Design: Multi-center prospective study.
Methods: Cranial samples of 249 patients (sagittal,100; coronal, 50; metopic, 49; and control, 50) were analyzed. Diagnosis was confirmed by the Seattle Children's Hospital on CT scan. Lambdoid synostosis cases were excluded because of scarcity. Patients with major medical problems, neurological conditions, and ≥3 minor extra-cranial malformations were also excluded. Cranial samples were collected during the reconstruction procedures. Control samples were collected from anonymous procedures or autopsy. The cranium was sliced into 3- to 5-mm sections and processed to extract RNA from osteoblast cells. Samples were analyzed on microarrays and gene information content (GIC) score, followed by Database for Annotation, Visualization, and Integrated Discovery pathway analysis. Keratinocyte growth factor-like protein 1 (*KGFLP1*) was also assayed.
Results: The suture-based gene expression patterns were compared to those of the control group. Only expression of fibroblast growth factor 7 (*FGF7*), vascular cell adhesion molecule 1 (*VCAM1*), and secreted frizzled-related protein 4 (*SFRP4*) were significant (P <0.05) and large. Forty-nine significant and large changes were seen in one or more forms of single synostosis compared to controls (36, coronal; 25, metopic; 14, sagittal). Changes in 19 genes (Venn regions m_1 and m_2) were consistent among 79% of metopic and 54% of coronal. Wingless-type MMTV investigation site family member 2 expression was found to be greater in coronal and metopic compared to control. Decreased insulin-like growth factor binding protein 2 expression was specific in coronal but not in metopic. Not only did metopic and coronal had significant differences relative to controls, but they also showed significant gene expression compared to sagittal. Twenty-five genes associated with extracellular matrix (ECM-mediated focal adhesion and 19 genes associated with ECM-receptor interaction were present in the modified KEGG pathway.
Conclusions: Metopic and coronal synostosis showed highly similarities, especially in Venn diagram, compared to sagittal synostosis. *FGF7*, *VCAM1* and *SFRP4* gene expression was present. This study shows an association between ECM-mediated focal adhesions and craniosynostosis.
Reviewer's Comments: This study shows that gene mutations result in single-suture synostosis. The gene mutations in sagittal gene mutations differ from coronal and metopic mutations, which correlate with previous animal data. The study can be expanded to further research into causes of craniosynostosis. (Reviewer-Tomoko Tanaka, MD).

Keywords: Single-Suture Craniosynostosis, Extracellular Matrix-Mediated Pathway

Print Tag: Refer to original journal article

Can Cervical Spine Screw Instrumentation Be Used in Children?

Feasibility of Intralaminar, Lateral Mass, or Pedicle Axis Vertebra Screws in Children Under 10 Years of Age: A Tomographic Study.

Cristante AF, Torelli AG, et al:

Neurosurgery 2012; 70 (April): 835-839

Screw instrumentation can be effective in pediatric upper cervical spine injuries.

Background: Screw placement in C1 and C2 are superior fixation devices compared to wire fixation techniques. However, screw fixation in pediatric upper cervical spine has limited practicably due to anatomical difficulties.
Objective: To measure dimensions in pediatric patients' C2 pars, pedicle, and lamina to determine feasibility of screw placement.
Design: Single-institution retrospective study.
Methods: Cervical CT scans performed at the Hospital das Clínicas of the University of São Paulo from June 2008 to June 2010 were reviewed on patients aged 2 to 10 years. Patients were divided into 2 groups by age; group 1 consisted of 23 cases between 24 and 48 months, and group 2 included 52 patients between 49 and 120 months. Measurements performed included dimensions and angulations of 88 laminas, pedicles, and lateral masses. Three patients were excluded due to fracture of C2.
Results: 75 CT scans were analyzed, including those of 45 male patients (60%) and 30 female patients (40%). The average age was 66.83 ± 28.93 months (group 1, 32 ± 9.06 months; group 2, 81.34 ± 20.79 months.) In group 1, only 5.5% of lamina and 8.3% of pedicles were <3.5 mm thickness. In group 2, only 1.2% of pedicles were <3.5 mm. No patient had lamina thickness <3.5 mm in group 2. All patients' lengths of lamina and pedicle and lateral mass were >12 mm. The spinolaminar angle was <41° in 5% of patients and was <51.8° in 90%. Both groups showed that the length of lateral mass was approximately 9 mm.
Conclusions: In both groups, most of patients had C2 lamina and pedicles with thickness >3.5 mm. The size of the 3.5 mm screw is the smallest in the currently available instrumentation systems. This study showed that C2 lamina and pedicle would be appropriate for the smallest screw instrumentation. The spinolaminar angles also are appropriate for instrumentation. No patient had lateral mass length too short to fit for the shortest (12 mm) screw.
Reviewer's Comments: This study analyzed the size of C2 in pediatric patients on CT scan. However, the study consisted only of CT scan measurements; patients did not receive actual instrumentation. While the measurement itself may be satisfactory for screw instrumentation, actual placement must be evaluated for adjacent anatomic features, such as the relationship of the vertebral artery to screw placement sites. Mechanical tolerance of pediatric bone to screw placement also needs to be addressed by in vivo studies. (Reviewer-Tomoko Tanaka, MD).

Keywords: Axis, Bone Screws, Spinal Fusion Tomography

Print Tag: Refer to original journal article

How to Do Well With a Brain Abscess

Supratentorial and Infratentorial Brain Abscesses: Surgical Treatment, Complications, and Outcomes -- A 10-Year Single-Center Study.

Landriel F, Ajler P, et al:

Acta Neurochir (Wien) 2012; 154 (May): 903-911

Advanced age, impaired immunology, and route of hematogenous transmission are associated with poor outcome of brain abscess.

Background: The incidence of brain abscess (BA) is 1 per 100,000 in developed countries. BA occurs more commonly in adult males between 20 and 40 years of age, followed by those 4 to 7 years old. Improvement in imaging studies and broad-spectrum antibiotics has resulted in earlier diagnosis and better treatment.
Objective: To review 10 years of BA cases in a single center.
Design: Single-center retrospective study.
Participants/Methods: 59 patients with 80 BAs underwent surgical treatment with either stereotactic aspiration or open craniotomy between February 2001 and January 2010. Surgical treatments were indicated for BA diameter >2.5 cm, mass effect from BA, BA located near the ventricle, progression despite antimicrobial treatment, and unclear etiology with neurological deterioration. Surgery was repeated if BA did not improve. Details of individual cases analyzed included Glasgow Coma Scale (GCS) score at admission, infection routes, and Glasgow Outcome Scale (GOS) score 6 months after surgery.
Results: The average patent age was 44.7 years (range, 0.16 to 77 years); 24 patients were male (40.7%). The median duration before diagnosis was 7 days. Presenting symptoms included fever (52.5%), headache (42.2%), focal neurological dysfunction (39%), increased intracranial pressure (32.2%), and seizures (23.7%). Mechanisms of infection included hematogenous (32.2%), contiguous transmission (23.72%), post-neurosurgical procedure (18.64%), and open traumatic brain injury (8.74%); 81.3% had favorable outcome (GOS of 5 points). Morbidity was 27.1%. Of the complications, 56.5% (9 patients) were minor (31.25% medical and 25% surgical). Eight patients were treated by medication. Twenty-five percent of patients had moderate complications (18.75% surgical and 6.25% medical); 18.75% were Grade III complications, related to multiple organ failure. Mortality (Grade IV) was 11.86%. Five of 7 patients (83.3%) died from medical causes. Twenty-three total patients (38.98%) had complications, and two thirds were related to medical problems. Seven patients (11.86%) required reoperation, and 5 did not have further complications. Two patients had new temporary neurological deficits after surgery. Younger age patients had favorable post-procedural outcome at 6 months, with mean age of 41.9 years with good outcome, compared to a mean age of 56 years with poor GOS scores. Of 11 immunosuppression patients, 5 had poor GOS. Hematogenous transmission had unfavorable outcome. *Streptococcus millieri* and Gram-negative bacilli (GNB) were the most common etiologic agents; 13.5% of cases did not grow any bacteria. The most common agents of postoperative BAs were GNB (27%), followed by anaerobes (18%). Open head traumatic injury was commonly *Pseudomonas*. Deep-seated BAs were associated with hematogenous (44.44%) and neurosurgery (22.22%) etiologies from GNB and methicillin-resistant *Staphylococcus aureus*.
Conclusions: Poor GOS at 6 months was correlated with advanced age, immunosuppression, and hematogenous transmission.
Reviewer's Comments: This paper focused on outcome 6 months after treatment of BA. Findings are not surprising. The paper provides a nice review of etiology, presenting symptoms, and outcome. Aggressive treatment is recommended for patients with poor predictors. (Reviewer-Tomoko Tanaka, MD).

Keywords: Brain Abscess, Complications, Outcome, Hematogenous Spread

Print Tag: Refer to original journal article

Calretinin Staining in ONB -- Another Entry in IHC Panel of Small Round Blue Cell Tumors

Calretinin Staining Facilitates Differentiation of Olfactory Neuroblastoma From Other Small Round Blue Cell Tumors in the Sinonasal Tract.

Wooff JC, Weinreb I, et al:

Am J Surg Pathol 2011; 35 (December): 1786-1793

Moderate to strong reactivity in >25% of tumor cells with calretinin and non-reactivity with p63, cytokeratin and desmin provide support for olfactory neuroblastoma in the context of small round blue cell tumors of the sinonasal tract.

Background: Olfactory neuroblastoma (ONB) is an important member in the differential diagnosis of small round blue cell tumors (SRBCT) of the sinonasal tract. This differential diagnosis arises with all too frequently scant biopsy material and the notoriously overlapping histology of other small round blue cell tumors. The histology of this tumor is composed of nests of small round cells within fibrovascular tissue. Some examples of neuroblastoma may contain the often-confused and misunderstood Flexner-Wintersteiner rosette (a true rosette more common in this malignancy) and the Homer Wright “pseudo” rosette (less common in this malignancy).
Objective: To explore calretinin and p63 in the diagnosis of neuroblastoma of the sinonasal tract.
Design: Retrospective study.
Participants: 63 patients with a diagnosis of SRBCT, including 21 patients with ONB and 42 patients with other SRBCT.
Methods: Reports were searched for ONB and SRBCT diagnosis. SRBCT cases included small-cell melanoma (5 cases), diffuse large B-cell lymphoma (5 cases), mantle cell lymphoma (1 case), extranodal NK/T-cell lymphoma--nasal type (4 cases), sinonasal undifferentiated carcinoma (6 cases), poorly differentiated neuroendocrine carcinoma not otherwise specified (1 case), moderately differentiated neuroendocrine carcinoma (1 case), small-cell neuroendocrine carcinoma (2 cases), alveolar rhabdomyosarcoma (4 cases), pituitary adenoma (3 cases), high-grade sinonasal non-intestinal type adenocarcinoma (1 case), teratocarcinosarcoma (1 case), non-keratinizing squamous cell carcinoma (2 cases), and extra-sinonasal Ewing's sarcoma/primitive neuroectodermal tumor (6 cases). Staining for calretinin and p63 was performed.
Results: Overall, 90% of ONB cases demonstrated moderate to strong reactivity with calretinin within >25% of malignant cells. This reactivity was localized to nuclear and cytoplasmic staining, and all cases of ONB were non-reactive with p63. Only cases of pituitary adenoma, small-cell neuroendocrine carcinoma, and the neuroepithelial component of the single case of teratocarcinosarcoma demonstrated a similar calretinin-positive and p63-negative immunophenotype.
Conclusions: Using clinical, histologic, and immunohistochemical features (including keratin, synaptophysin, chromogranin and S-100), the differential diagnosis of SRBCT can be refined. As smaller lesions are detected and smaller biopsies are obtained, differentiating SRBCT may be aided by the use of (1) calretinin and p63 staining, and (2) strict interpretation of these stains with regard to result. Moderate to strong staining within >25% of neoplastic cells with calretinin, nonreactivity with p63, and an otherwise compatible immunohistochemical profile can offer support for ONB over the other members within this complicated differential.
Reviewer's Comments: ONB versus SRBCT is a vexing differential diagnosis. These cases are difficult due to poor or scant sampling, crush artifact, and conflicting immunohistochemical profiles that are tempting to interpret as “poorly differentiated neoplasm.” The authors include immunohistochemical analysis of a variety of cases within the differential diagnosis. The authors demonstrate utility for calretinin and p63 in the diagnosis of ONB, especially in cases with marginal immunohistochemistry. (Reviewer-Frank N. Moore, MD).

Keywords: Esthesioneuroblastoma, ONB, Calretinin, p63, IHC, Small Round Blue Cell Tumors, Sinonasal

Does Thrombolytic Tx Affect Favorable Outcomes Post-Ischemic Stroke?

Thrombolytic Treatment of Patients With Acute Ischemic Stroke Related to Underlying Arterial Dissection in the United States.

Qureshi AI, Chaudhry SA, et al:

Arch Neurol 2011; 68 (December): 1536-1542

The rate of intracranial bleeding after thrombolysis is no higher among ischemic strokes caused by arterial dissection than among those caused by other arterial diseases.

Objective: To determine the risks and benefits of thrombolytic treatment of ischemic stroke caused by arterial dissection.
Design: Retrospective study.
Methods: The National Inpatient Sample, a large administrative database derived from inpatient stays in 1000 U.S. hospitals, was the source of information. Available data included diagnoses, procedures, demographic information, and hospital discharge status. The latter was used as a surrogate for clinical outcome. Odds ratios (ORs) of outcomes were adjusted by multivariate analysis for many confounding variables, including age, sex, hypertension, and diabetes.
Results: Among 47,899 patients treated by thrombolysis for ischemic stroke from 2005 to 2008, 488 (1%) had arterial dissection, but location (extracranial or intracranial, anterior or posterior circulation) and NIH Stroke Scale scores were unknown. Most patients were treated with intravenous thrombolysis, but more than 3 times as many with dissection (32%) were treated with intra-arterial thrombolysis as those without dissection (9%). The rate of subarachnoid and cerebral bleeding after thrombolysis was no higher in patients with dissection (6.9%) than in those without dissection (6.4%). The rate of moderate to severe disability upon hospital discharge (poor outcome) was higher among the patients with dissection than those without it (OR, 2.8; 95% CI, 1.7 to 4.6; *P* <0.001). The same was true, however, among the 3 million stroke patients with and without dissection who were not treated with thrombolysis.
Conclusions: The rate of intracranial bleeding after thrombolysis is no higher among ischemic strokes caused by arterial dissection than among those caused by other arterial diseases. The functional outcome of stroke caused by arterial dissection is worse than that of stroke caused by other diseases, whether treated by thrombolysis or not.
Reviewer's Comments: The risk of subarachnoid hemorrhage in intracranial vertebral-artery dissection is thought to be higher than that in intracranial carotid dissection, but this study lacks the data to determine whether thrombolysis increases the relative risk. It also lacks the data to determine whether there is any benefit of thrombolysis in stroke due to arterial dissection. (Reviewer-Marc David Winkelman, MD).

Keywords: Thrombolysis, Ischemic Stroke, Arterial Dissection

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