Crossover and clinical outcomes in the Barrow Ruptured Aneurysm Trial

To The Editor: The article by Dr. Spetzler and colleagues\(^5\) on the Barrow Ruptured Aneurysm Trial (BRAT) (Spetzler RF, McDougall CG, Albuquerque FC, et al: The Barrow Ruptured Aneurysm Trial: 3-year results. Clinical article. J Neurosurg 119:146–157, July 2013) provided us with interesting reflections regarding the choice of treatment for ruptured aneurysms.

In the International Subarachnoid Aneurysm Trial (ISAT), randomization of patients with subarachnoid hemorrhage (SAH) was appropriate for those harboring aneurysms judged to be suitable for either coiling or clipping based on the angiographic anatomy when clinical equipoise existed in these patients.\(^4\) The patient population in ISAT represented only a subgroup of patients, specifically those whose SAH was deemed a good grade and whose anterior circulation aneurysm was less than 10 mm in diameter.\(^1,2\) One reason the ISAT authors posited to explain their relatively low enrollment rate was a lack of equipoise on the part of neurointerventionists and neurosurgeons responsible for recruiting patients.\(^3\)

To cope with these limitations of the ISAT, the BRAT study was designed to enroll all patients with acute nontraumatic SAH without the criterion of equipoise selection.\(^2\) Compared to ISAT, this design led to a greater proportion of patients being randomized in BRAT (nearly 65%) and to a sample population that was more diverse with respect to SAH grade and aneurysm location and size. However, as a consequence of the all-inclusive protocol in BRAT, a large proportion of patients in the coil-assigned group whose lesions were considered unsuitable for coiling did cross over to clipping (38%). This reflected the fact that fewer patients were deemed eligible for either treatment than patients judged suitable for clipping overall.

The intention-to-treat analysis in BRAT counted crossover patients with their originally assigned group regardless of what treatment was actually received. Results at the 1-year follow-up demonstrated that the mean patient outcome in the coil-assigned group (modified Rankin Scale Score \(>2\)) was not as poor as that in the clip-assigned group (OR 1.68, 95% CI 1.08–2.61; \(p = 0.02\)).\(^2\) A subgroup analysis that excluded crossover patients showed even better outcomes in the coil-coil group than in the clip-clip group (OR 2.28, 95% CI 1.30–4.13; \(p = 0.005\)).\(^2\) This disparity could be attributed to the poorer mean outcome in patients who crossed over from clipping to clipping therapy than in patients who received their assigned coiling treatment (33.9% vs 18.4% of poor outcome, respectively). If the clip-clip crossover group had had an even worse mean patient outcome, it would be fair to think that the benefit of coiling shown in the intent-to-treat analysis at 1 year would have been lost.

In the 3-year follow-up BRAT paper,\(^2\) the difference in the primary outcome between the coil-assigned and clip-assigned groups was no longer significant. However, the authors did not comment on whether the subgroup analysis that excluded crossover patients at 3 years of follow-up still favored a better outcome for the coil-coil group.\(^5\) In fact, although the results are displayed in Table 2, the \(p\) value in the footnote is missing a number: “Coil-coil compared to coil-clip at 3 years: \(p = 0.007\). Coil-clip compared to clip-clip at 3 years: \(p = 0.26\). Coil-coil compared to clip-clip at 3 years: \(p = 0.0\).” Interestingly, the mean patient outcome in the coil-clip crossover group worsened at 3 years compared with the mean outcome at 1 year (42.2% vs 33.9% poor outcome, respectively). It would be interesting if the authors would discuss the worsening of outcome in the coil-clip crossover group to explain the loss of statistical difference in the primary outcome at 3 years. Was there a bias created toward the null hypothesis when the mean outcome in the coil-clip crossover group became worse? Large crossover in randomized studies decreases statistical power, an effect that is amplified by long-term analysis when more patients are lost to follow-up, their outcomes change, or they die.\(^5\)

Secondarily, an erratum should be issued for a typographical error. In the Methods section of the abstract, the word “coiling” should replace the word “clipping” at the end of the following sentence: “Of the 170 patients who had been originally assigned to coiling, 64 (38%) crossed over to clipping, whereas 4 (2%) of 179 patients assigned to surgery crossed over to clipping.”

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Disclosure

The author reports no conflict of interest.

References


RESPONSE: We thank Dr. Denis for his careful review of our article and his most thoughtful questions. His points are clearly made and his questions appropriate and well taken.

We will address Dr. Denis’s points in order, beginning with his observation that “if the coil-clip crossover group had had an even worse mean patient outcome, it would be fair to think that the benefit of coiling shown in the intent-to-treat analysis at 1 year would have been lost.” We agree that the impact of crossing patients from the coiling to clipping procedure was to diminish the size of the treatment effect measured, in effect diluting the benefit. The significance of this must be interpreted with caution, however, as patient selection for crossover was not made randomly. While it is true that patients who crossed over to clipping treatment fared worse than patients who did not cross over, it is not assured that their outcomes would have been better had they, in fact, been treated with the coiling procedure to which they were initially randomized.

Next, with respect to the subgroup analysis at 3 years for “coil-coil compared to clip-clip” treatment, the mean outcomes in these two groups did remain statistically significantly different, with the difference continuing to favor coiling at 3 years. Twenty-four (22.6%) of 106 patients randomized to coil therapy and treated by coiling and 60 (34.3%) of 175 patients randomized to clip therapy and treated by clipping had poor outcomes. We regret that the p value of 0.04 for this comparison was inadvertently omitted from Table 2. We are correcting this omission and the typographical error that Dr. Denis observed, and we are noting these changes in an erratum notice. Again, caution is needed in interpreting this subgroup analysis, as the two groups in question were not randomly chosen. The “clip-clip” group certainly contained some patients who would have been excluded from coil therapy had they been randomized to that treatment arm.

Regarding the deterioration in outcomes observed between Years 1 and 3 among patients who originally were assigned to coiling but crossed over to clipping, the small sizes of the groups mean that a large percentage change is accounted for by a relatively small number of patients. Worse outcomes occurred in 22 (33.9) of the 65 patients in the coil-clip group at 1 year, but by 3 years the number of poor outcomes in this group had increased to 27 (42.2%) of the 64 patients. This 8.3% change resulted from deterioration in the condition of 5 patients in this group between Years 1 and 3. The deteriorations in condition were due to lung cancer in 1 patient and progression of dementia in 1 elderly patient. The conditions of the remaining 3 patients deteriorated from modified Rankin Scale Score 2 to Score 3, with all patients citing symptoms relating to difficulties with concentration, memory, and depression. One of these three, a patient with a history of psychiatric illness and substance abuse, reported new strokes but would not cooperate with our attempts to obtain more detailed follow-up.

This observation is interesting, but given what is known about the causes of the deterioration in these patients, it does not seem influential in recommending one treatment modality over another. In essence, it again highlights the limitations of an underpowered trial, and, in particular, brings to light the hazards of examining subgroups that were not specified beforehand. It is reasonable to use such data to generate hypotheses, but post hoc choices for subgroup analysis and limited statistical power should preclude overinterpretation of these results.

In the final analysis, the primary outcome of BRAT credibly demonstrated that a policy of coiling as a first choice led to fewer poor outcomes 1 year after treatment. Subsequent subgroup analysis does not change this result, but legitimately raises questions as to why this occurred. Similarly, at 3 years, failure to detect the continued statistically significant benefit of the primary outcome raises questions as to whether, in fact, the benefit was lost or rather that the study simply lacks the statistical power needed to detect a narrowed margin of benefit.

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Complications with cranial perforators

To The Editor: We read with great interest the paper on intraoperative complications of cranial perforators by Vogel et al.1 (Vogel TW, Dlouhy BJ, Howard MA III: Don’t take the plunge: avoiding adverse events with cranial perforators. Clinical article. J Neurosurg 115:570–575, September 2011). The authors describe the complications in using cranial perforators during a 2-year period in 1652 cranial procedures. Plunging, defined as “an uncontrolled rapid increase in depth of the cranial perforator or drill,” occurred in 9 procedures (0.54%). This overall complication rate is relatively low, and plunging in these 9 cases did not result in any serious or irreversible damage to the patient.

Trephining the skull is one of the basic skills that must be acquired during neurosurgical training. There are various methods of performing a craniotomy, all starting with 1 or multiple holes.1 These holes can be created using mechanical, electrical, or pneumatic devices, and the size and method of the bur hole vary among the

This article contains some figures that are displayed in color online but in black-and-white in the print edition.
chosen techniques. Multiple aspects must be considered when choosing the method of trephining, including the 1) complications associated with the applied technique, 2) the speed of the technique, 3) the cosmetic result, and 4) cost.

In January 2010, one of the authors (T.M.) switched from using a cranial perforator (such as the one described in the abovementioned study) to a high-speed drill for making bur holes. The rationale for this change was 3-fold: economic, educational, and cosmetic. Concerning the economic issue, a single-use disposable perforator (Codman, Johnson & Johnson) costs around €146 (approximately $195 US) in Belgium. As an alternative, a regular surgical cutting ball drill of 4 mm (Midas Rex, Medtronic) costs around €77 (approximately $103 US) and can be resterilized 8–10 times, reducing the cost to approximately €10 per procedure. The economic burden of using these disposable cranial perforators may seem irrelevant; however, the total cost per year may change views on this subject at a time when economic aspects of general health care costs are of concern. In our clinic, the use of a high-speed drill reduced the cost for craniotomies and bur hole procedures (for 1 surgeon performing around 200 bur holes and craniotomies together per year) to approximately €18,000 (approximately $24,000 US) per year.

Considerations other than cost, namely educational and cosmetic, may also motivate the more routine use of a high-speed drill for trephining the skull. If residents are consequently trained to drill bur holes with a high-speed drill in a relatively safe area, such as for ventriculostomy procedures or pterional craniotomies, then they are better prepared to drill and have better control of movements in a more difficult and critical surgical field (for example, drilling the internal acoustic meatus or anterior clinoid process).

Finally, customized drill holes are usually smaller than the regular 11-mm bur hole resulting from the cranial perforator (Fig. 1). A Codman disposable perforator makes bur holes of 9, 11, or 14 mm (depending on the size of the perforator), as compared with the 5- to 7-mm bur holes made using the high-speed drill. Bur holes in the frontal area especially can give disappointing cosmetic results, and decreasing the size of the bur hole may give superior cosmetic results after the craniotomy. Moreover, the bur hole can be adapted to the scheduled craniotomy, for example, extending the bur hole in a curvature (Fig. 2) or drilling in a specific configuration for the placement of extended neuromonitoring probes (Fig. 3).

We realize that making bur holes using a high-speed drill may already be common practice among neurosurgeons and that its use is dependent on local habits and preferences.

In conclusion, it is our opinion that the use of a high-speed drill is a good and cost-effective alternative to the cranial perforator for drilling bur holes. Nevertheless, the authors are to be congratulated for reporting the complication rate for a product routinely used in a neurosurgical practice.

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Fig. 1. View of a high-speed drill and a medium-sized cranial perforator.

Fig. 2. Intraoperative view of bur holes made with a high-speed drill (left) and cranial perforator (right) for a right-sided pterional approach.

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Disclosure

The authors report no conflict of interest.
Cell transplantation


Cell transplantation is a well-established strategy in repair of peripheral nerve defects. Berrocal et al.1 explored the transfer of Schwann cells in collagen conduits for the reconstruction of large, segmental peripheral nerve defects to improve the axonal growth in rats. At 4-week and 16-week observation points they found green fluorescein protein–expressing Schwann cells along the length of the nerve guide that they had placed within the large (13-mm) nerve defects that they created in rats’ sciatic nerves. Based on histological and functional evidence, they showed promising results with excellent regeneration of peripheral nerve.

In human patients, the grafted nerve cannot be resected to perform histological staining. Importantly, electromyography, measurement of nerve conduction velocity, and evoked potential studies are used in clinical practice for assessing nerve function. Combining electrophysiological studies with functional evaluations would provide side-by-side longitudinal assessment of nerve regeneration in the authors’ rat model before translation into human trials.

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Reference


RESPONSE: We would like to thank the authors for raising very important points regarding our laboratory investigation on the transplantation of Schwann cells in a collagen tube for the repair of large segmental peripheral nerve defects in rats. Our group demonstrated that adding Schwann cells to a guidance channel enhanced the gap distance that can be repaired after peripheral nerve injury with long segmental defects. We believe that this finding is an important contribution toward the goal of bringing autologous Schwann cell–based therapies to the domain of peripheral nerve injuries with long segmental defects in a clinical setting.

We also agree that additional electrophysiological studies need to be incorporated along with the functional and histological evaluations presented. We have previously shown that repair of somewhat shorter gaps (9 mm) with channels containing autologous Schwann cells in the cauda equina of cynomolgus monkeys can lead to low threshold stimulus evoked electromyographic responses1 after a 10-month survival period. We do appreciate the feedback and will incorporate additional functional assessments including electrophysiological studies to address some of the final and critical steps that will bring autologous Schwann cell transplantation to human patients.

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Cerebrospinal fluid leak


Cerebrospinal fluid leak is one of the serious complications after endonasal endoscopic transsphenoidal resection of a sellar tumor. It may lead to headache, meningitis, venous stretch, and intracranial hematoma. Dlouhy et al.1 conducted a retrospective study to evaluate the correlation between body mass index (BMI) and postoperative CSF leak. They found that an elevated BMI is an independent predictor of postoperative CSF leak after an endonasal endoscopic transsphenoidal approach.

This is a very interesting issue. It prompted us to further consider what kind of comorbidities would correlate with postoperative CSF leak. We would like to suggest that there is a need for further investigation with respect to the following 3 topics and their relationships to postoperative CSF leak: 1) metabolic syndrome–associated hypertension; 2) sleep apnea and exertional respiration leading to early postoperative shift of repaired tissue fragments prior to healing; and 3) poor wound healing due to diabetes mellitus.

The study by Dlouhy et al. showed an important finding of a significant association between postoperative CSF leak and elevated BMI and reminds neurosurgeons to pay high attention to CSF leak in patients with a high BMI. Prospective multi-center analyses of the risk factors contributing to postoperative CSF leak are warranted.

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Disclosure

The authors report no conflict of interest.

Reference


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The authors report no conflict of interest.

References


Response: We appreciate the letter written by Lanzino and colleagues and read with interest the case illustrated therein. In addition to suspecting a complex dissecting pseudoaneurysm of the posterior communicating/posterior cerebral artery, the diagnosis of a congenital intracranial dilative arteriopathy could have been considered in this young patient. Contributing factors such as genetic, inflammatory, immunological, and degenerative condi-

Pure arterial malformations of the posterior cerebral artery

To The Editor: We read with great interest the report by McLaughlin et al.¹ (McLaughlin N, Raychev R, Duckwiler G, et al: Pure arterial malformation of the posterior cerebral artery: importance of its recognition. Case report. J Neurosurg 119:655–660, September 2013) on pure arterial malformations of the posterior cerebral artery. We would like to briefly illustrate a similar case that supports these authors’ claim that indeed the vascular anomaly described may represent a separate pathological entity. In August 2010, a 10-year-old girl complained of a short-lasting, primarily left-sided headache that woke her up from sleep. Axial imaging studies did not show any acute bleeding but raised the suspicion of a complex vascular anomaly involving the supraclinoid internal carotid artery (ICA). This was confirmed by a subsequent catheter angiography (Fig. 1). After seeking multiple opinions, she was referred to our institution. We interpreted the lesion as representing a possible complex dissecting pseudoaneurysm of the posterior communicating/posterior cerebral artery and proceeded to perform coil embolization of the larger, saccular-type, pseudoaneurysm component. Three years later, the girl remains well and very active in various sports. Axial imaging studies have shown stability of the lesion over time.

Years ago, William Sweet wrote a thoughtful article on the difference between one and zero and how new concepts and descriptions of pathological conditions often start with a single observation not always fully appreciated by the unprepared mind.² The striking resemblance between the case reported by McLaughlin and coworkers and our case seems to indeed confirm, as boldly proposed by these authors, that we may be dealing with a separate pathological entity. We commend the authors for their keen observation, and we encourage more reports of similar cases so that the natural history and the true clinical significance of this entity can be better defined.

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Disclosure

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tions should be sought. However, we agree with Lanzino and colleagues that the case they shared is similar to the pure arterial malformation we reported.

Since the time of publication of our case report, we encountered an additional patient with a vascular lesion suggestive of a pure arterial malformation. An 8-year-old girl was referred for management of an arteriovenous malformation. At age 3 years, she underwent head imaging (CT and CT angiography) in the context of a sinus infection. Her neurologist diagnosed a brain arteriovenous malformation and recommended conservative treatment. Five years later, after having experienced new episodes of isolated headaches in the absence of other symptoms, the patient underwent new brain imaging (CT angiography and MR angiography). At this time, there was no significant change in the mass of the coiled abnormal vessels in comparison to previous images. Contributing factors to congenital intracranial dilative arteriopathy had been sought and ruled out by her neurologist. An angiogram was recommended to better characterize the abnormal vessels. The angiogram again showed the dilated supraclinoid left ICA and proximal aspect of the left M1 segment (Fig. 1). Supporting the hypothesis that this was a pure arterial malformation, the dilative appearance extended beyond the main vessel (ICA and M1), involving the origins of the left ophthalmic artery, left anterior choroidal artery, and left lateral lenticulostriate arteries. Similar to the case we reported and the case shared by Lanzino and colleagues, this additional case also had a saccular aneurysm arising from the supraclinoid segment of the left ICA. Given the superposition of tortuous vessel and the difference in technique, it was challenging to determine if the aneurysm was present on previous images acquired at outside facilities. The patient was managed conservatively and recommended to undergo follow-up catheter angiography with 6-second frames and 3D acquisition in 9 months.

Other cerebrovascular surgeon colleagues have written to the senior author (N.A.M.) following the publication of the case report on pure arterial malformations, recollecting similar cases in their practice. In order to better study the natural history and clinical significance of this new entity, we propose the coordination of a registry of such potential cases. We thank Dr. Lanzino and colleagues for sharing their case and encourage others to

**Fig. 1.** Sequential arterial phase lateral (A–C), anteroposterior (D), and 3D (E) angiograms of the left ICA show a complex vascular anomaly involving the posterior communicating artery. Anteroposterior left vertebral artery angiogram (F), obtained during balloon test occlusion of the left ICA, demonstrates the abnormally dilated caliber of the proximal left posterior cerebral artery (arrow) and the anomaly involving the posterior communicating artery. The patient underwent uneventful coil embolization of the larger, pseudoaneurysm component (G), which resulted in flow disruption and contrast stasis (arrowhead, H) into this component.

**Fig. 1 (Response).** Lateral (left) and anteroposterior (right) left common carotid artery injection angiograms acquired via femoral catheter, showing the dilated supraclinoid left ICA and proximal aspect of the left M1, representing a coiled mass of dilated elongated and tortuous vessels with no early venous drainage, suggestive of a pure arterial malformation.
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report other descriptions of similar cases and to consider entering the case in the ongoing registry.

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Decompressive craniectomy

To The Editor: We read with some interest the paper by Kenning and colleagues (Kenning TJ, Gooch MR, Gandhi RH, et al: Cranial decompression for the treatment of malignant intracranial hypertension after ischemic cerebral infarction: decompressive craniectomy and hinge craniotomy. Clinical article. J Neurosurg 116:1289–1298, June 2012), in which the authors retrospectively compared hinge craniotomy with decompressive craniectomy for the treatment of malignant intracranial hypertension after ischemic cerebral infarction. This study demonstrated that both hinge craniotomy and decompressive craniectomy achieve sufficient reduction in intracranial pressure, and that cranioplasty is almost never needed in the hinge group, which significantly prevents the associated morbidity.

However, we strongly object to the conclusion that the long-term functional outcome was better in the hinge craniotomy group. For this comparison, the authors left out of the analysis all patients who died, which is scientifically unsound. The mortality was increased 4-fold in the hinge craniotomy group (11% vs 44%), and removing these patients creates a severe bias toward a better outcome in the hinge craniotomy group.

As a comparison, in the original meta-analysis of the efficacy of decompressive craniectomy for malignant middle cerebral artery infarction, the proportion of patients with a good functional outcome (modified Rankin Scale Score 0–3) was higher in the decompressive craniectomy group than in the conservative treatment group (43% vs 21%). However, if these calculations are performed without including the deceased patients, the outcome would appear to be better in the conservative group (55% and 75% for the decompressive craniectomy and conservative groups, respectively). Obviously, this apparent result is not because conservative treatment is superior, but solely due to the fact that, similar to the study by Kenning et al., the mortality was much higher in the conservative treatment group.

In conclusion, we think that the statistics describing the differences in clinical outcome are inappropriate. The primary goals of the procedure, intracranial pressure reduction and secondary cranioplasty prevention, seem to be well reached. The effect on functional outcomes, as the authors rightfully mention, will have to be studied in a larger prospective cohort, the results of which we eagerly await.

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Disclosure

The authors report no conflict of interest.

References


Response: No response was received from the authors of the original article.

Diffuse low-grade gliomas and UCSF scores

To The Editor: We enjoyed reading the letter by Jakola and coworkers (Jakola AS, Unsgård G, Kloster R, et al: Diffuse low-grade gliomas. J Neurosurg 119:1354–1355, November 2013 [Letter]) related to our recent article on the spontaneous and therapeutic prognostic factors in adult hemispheric WHO Grade II gliomas. They emphasized early and maximal safe resection as the primary strategy for WHO Grade II gliomas, and they refined discriminating values of the University of California, San Francisco (UCSF), scoring system. We agree with these points that were highlighted in our article.

In particular, they found the distribution of the UCSF score to vary markedly between the study by Jakola et al. (the so-called Norwegian study) and the study by Capelle et al. (the so-called French study) and asked for potential selection bias in the French study. First, we wish to clarify the distribution of the USCF score in the population of our French study in which we reported a low-risk group, which combined UCSF Scores 0 and 1 (reported as Score 0 in the article), an intermediate-risk group, which included UCSF Score 2 (reported as Score 1 in the article), and a high-risk group, which combined UCSF Scores 3 and 4 (reported as Score 2 in the article). There is, in fact, a good amount of overlap in the distribution of the UCSF scores between the Norwegian and the French studies, as detailed in Table 1. Second, our French study selected cases from a large database of a multicenter, multidisciplinary French glioma study group (Réseau d’Étude des Gliomes, REG) that were collected retrospectively from 1985 to 1996 and prospectively since 1996. The patient selection was population based in the participating centers with inherent bias. Similar results and conclusions were drawn in our French
study and in the population-based Norwegian study. Third, we advocate a case mix for meaningful comparative multicenter studies.

**Disclosure**

The authors report no conflict of interest.

**References**


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**SEER analysis and statistical judgment**

To The Editor: We read with interest the article by Stessin et al.13 (Stessin AM, Schwartz A, Judanin G, et al: Does adjuvant external-beam radiotherapy improve outcomes for nonbenign meningiomas? A Surveillance, Epidemiology, and End Results (SEER)–based analysis. Clinical article. J Neurosurg 117:669–675, October 2012), which suggested that neither external-beam radiotherapy (RT) nor the extent of surgery confers any survival advantage in patients with non–WHO Grade I meningiomas. However, modern, well-documented RT and surgical series have suggested that adjuvant RT and optimal surgery do indeed improve local control.1,5,6 Moreover, we are aware of 8 studies demonstrating that anatomical tumor location is not correlated with patient outcome7–11 and 3 studies demonstrating the positive effect of gross-total resection on survival.2,3,11 The conclusions of Stessin et al. run counter to existing prognostic concepts for these nonbenign tumors. Notwithstanding the limitation of SEER analyses, these authors engaged in an extravaganza of subgroup analysis and statistical speculations resulting in data sets that are no longer generalizable.

Firstly, one of the key principles in epidemiology is generalizability or similarity between patients in the analyzed data set and those in the entire patient population. Between 1973 and 2007, there were 1259 listed meningiomas in the SEER database. The authors then engaged in the creation of many subsets of data, in some cases because of missing data (some data sets are numerically questionable with a low sample size of 56–82 patients). When using the case deletion method to handle missing data, the authors made the assumption that the missing data were random and that the remaining patients were essentially the same as those who were deleted—an important and dangerous assumption that can lead to erroneous results.

Secondly, contrary to data in other recent studies, the findings of Stessin et al. demonstrated a radical relationship between anatomical tumor location and survival. Their hazard ratio (HR) was 0.024 with a 95% CI interval of 0.002–0.233, which can be inverted to an HR of 41.6 with a 95% CI of 4.3–500; the latter has an upper/lower confidence interval ratio of 116, which is extremely unstable. In addition, the authors did not find gross-total resection to be a positive prognostic factor. And, most importantly, they concluded that radiotherapy does not alter the prognosis of such a patient. These questionable findings can be evidence of bias stemming from coding difficulties with this particular tumor or the unorthodox subsetting procedures, which can indeed influence the analysis.

Parsimony rules in epidemiology, and as demonstrated here, every step that increases the complexity of an analysis threatens the validity of the subsequent results. Through the use of complex subsetting procedures and a database that is primed for population-based research rather than treatment-efficacy research, Stessin et al. produced some erroneous and incongruent results. They should have used either a sensitivity analysis or multiple imputation and presented their data as done by Ressegueir et al.12

We fully concur with the authors’ conclusion that the prospective data stemming from the RTOG and EORTC cooperative groups14 will be of critical importance for the management of these challenging tumors.
Neurosurgical forum

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CD97 and glioma invasion


Malignant glioma carries a poor prognosis despite aggressive resection and combined chemoradiotherapy.2-5 Therefore, the investigation of molecular targets2-5 is crucial to find some potential therapeutic modulations. Chidambaram et al.1 conducted a glioma cell line–based study using a short interfering RNA approach to investigate the function of WT1 and CD97 by means of quantitative reverse transcription polymerase chain reaction, Western blotting, and Matrigel invasion assay.

Their study supports a novel role for CD97 in glioma cells, especially with respect to the invasiveness of glioma cell lines.1 However, the properties of cell lines may change when the cells are removed from the in vivo microenvironment. Future experiments through the immunohistochemical staining of various grades of human glioma and non-tumor tissue control would provide more solid evidence of a role for CD97 in glioma invasiveness in humans. Moreover, study of CD97-expressing cells in xenograft is warranted to investigate whether CD97-expressing cells are present in the invasive front.

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Disclosure

The authors report no conflict of interest.

References

**Deep brain stimulation and microelectrode recording**

**To The Editor:** We read with interest the recent publication by Burchiel et al.1 (Burchiel KJ, McCartney S, Lee A, et al: Accuracy of deep brain stimulation electrode placement using intraoperative computed tomography without microelectrode recording. Clinical article. *J Neurosurg* 119:301–306, August 2013). The authors suggest that performing subthalamic nucleus (STN) deep brain stimulation (DBS) with intraoperative CT and the NexFrame system (Medtronic, Inc.) can achieve a high level of accuracy (mean vector error 1.59 mm, trajectory deviation 1.24 mm). The 60 patients in the study were placed under general anesthesia and did not undergo microelectrode recording (MER). The authors found a statistically significant negative correlation between the distance of the electrode trajectory to the closest lateral ventricular wall and planning accuracy. We are conducting an ongoing study of various imaging strategies for STN DBS planning, which makes us interested in this report.

Previous studies have shown that planning with MRI usually carries a risk of image distortion. Our previous experience confirmed the benefit of the image fusion technique with stereotactic CT and MRI in frame-based DBS surgery, leading to a longer recorded length of the STN and more single-trajectory recording during MER.2 Using composite-planning methods with 3-T MRI, Toda et al. also achieved a more accurate electrode position.7 These findings all echo highlights of the study by Burchiel et al., and we may need to adopt more imaging modalities to prevent catastrophic accidents with DBS, such as intracranial hemorrhage and electrode malposition.6,8

Another interesting point is the extent to which the distance of the electrode trajectory to the ventricle influences the planning error and postoperative outcome. Ventricle penetration has been correlated with higher risks of postoperative morbidity and should be avoided.3 In addition, T2-weighted images have also revealed greater distortion of the lateral ventricle.5 Since most direct targeting depends on T2-weighted MRI, the study by Burchiel et al. further emphasized the importance of precise delineation of ventricles.

We also performed STN DBS under general anesthesia. However, our team greatly relied on MER, which allowed more accurate electrode positioning and better clinical outcomes, but with a possible longer operative time.4 In addition, MER not only confirms the STN position but also helps characterize the STN topography and neurophysiological function.

Given that more neurosurgeons adopt the first tract as the final implantation site and the risk of intracranial hemorrhage is never forgotten during MER, more centers have chosen intraoperative imaging (CT or MRI) to verify electrode positioning, and MER may not be necessary. Accurate localization of the target nucleus and stimulating electrode placement are prerequisites to successful outcome for stereotactic neurosurgery. We can anticipate that more imaging modalities and anesthesia methods could provide our neuropsychiatric patients a comfortable operative experience without compromising surgical outcomes.

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**References**


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