Glioblastoma

To The Editor: We are very interested in the laboratory investigation by Ju et al.1 (Ju H, Li X, Li H, et al: Mediation of multiple pathways regulating cell proliferation, migration, and apoptosis in the human malignant glioma cell line U87MG via unphosphorylated STAT1. Laboratory investigation. J Neurosurg 118:1239–1247, June 2013).

Glioblastomas multiforme are characterized by high invasiveness, rapid proliferation, and resistance to apoptosis. Therefore, the investigation of a novel therapy is very important. Ju et al.1 explored the effect of overexpression of the signal transducer and activator of transcription 1 (STAT1) protein on apoptosis, migration, and proliferation of the U87 glioma cell line. They concluded that STAT1-transfected U87 glioma cells decreased proliferation, suppressed migration, and increased apoptosis.

First, they did not show a fundamental result of the STAT1 band in the Western blot analysis in Fig. 2C to convince readers that the STAT1 was really well transfected into U87 glioma cells. To address this point, we suggest they could put the result of STAT1 Western blot analysis in their response to this letter. Moreover, as shown in the left panel of Fig. 2C, the expression level of cleaved caspase-3 seems not significantly higher in STAT1-transfected U87 glioma cells than in the mock or vector control groups in the Western blot analysis.

Despite these minor limitations, their findings raised the possibility of an important role of STAT1 in glioblastoma, suggesting that STAT1 overexpression is one of the therapeutic targets in human gliomas. Further studies performed using in vivo stereotactic orthotopic xenografts to investigate the effect of STAT1 overexpression on survival and tumor size are warranted.

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Disclosure

The authors report no conflict of interest.

Reference


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

Gamma Knife surgery

To The Editor: We read with interest the recently published article by Salvetti et al.5 (Salvetti DJ, Nagaraja TG, McNeill IT, et al: Gamma Knife surgery for the treatment of 5 to 15 metastases to the brain. Clinical article. J Neurosurg 118:1250–1257, June 2013). We were surprised that the authors omitted reference to our earlier work in the management of multiple brain metastases using Gamma Knife surgery (GKS), which was published in the Journal of Neurosurgery in 2002.2 In that paper we reported on 72 patients with more than 10 brain metastases from different primaries, including but not limited to lung cancer, breast cancer, melanoma, and renal carcinoma treated with GKS. A total of 147 treatment sessions were required to treat 1304 sites in the 72 patients. The mean tumor volume was 1.7 cm3. The median number of tumor sites during the first treatment session was 11.

We noted in a multivariate survival analysis that the most significant prognostic factors for improved survival were 1) female sex, 2) total tumor volume < 30 cm3, and 3) Karnofsky Performance Scale score higher than 70. The origin of the primary neoplasm, patient age, radiosurgical dose, and previous whole-brain radiation therapy were not significant. The total intracranial tumor volume treated was of greater prognostic significance than the absolute number of metastases treated. In our previously published study2 of 22 patients with brain metastases from renal cell carcinoma, in which we treated with GKS an average of 6 lesions per patient, we achieved local control in 20 patients. In another previously published series of 68 women with breast cancer metastatic to the brain, we treated 26 patients with 1–3 lesions, 18 patients with 4–7 lesions, and 24 patients with 8 or more lesions.3

On a somewhat related note, in the editorial for Salvetti and colleagues’ article,4 the observation that the current payment paradigms limit reimbursement at 5 tumors is not valid in the state of Florida. In our state, Gamma Knife procedures are not reimbursed by the number of lesions treated, but instead by the number of treatment sessions performed.

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The authors report no conflict of interest.

References

RESPONSE: We thank Drs. Wolf and Amendola for their interest in the article on 5–15 brain metastases and the accompanying editorials. Their early research in the field along with others', including the pioneering work of Dr. Yamamoto and colleagues, helped to expand indications for stereotactic radiosurgery. In their study published in a supplement to the Journal of Neurosurgery, it is important to note that most patients had stereotactic radiosurgery in 2 or more sessions and that the number of metastases managed in the first radiosurgery ranged from 1 to 30. The timing of initial and subsequent radiosurgeries was not specified in this publication. The current study reflects contemporary practice using the Gamma Knife to treat all brain metastases visible on MRI (5 or more) in a single session.

As the indications for radiosurgery expand, the reimbursement will also need to be commensurate. After all, if one does two craniotomies in a single patient at one sitting, the neurosurgeon is reimbursed for both procedures. At radiosurgery, each tumor in a different location can have different clinical manifestations and ramifications, require a different preoperative discussion related to potential outcomes and risks, involve more work during the radiosurgery, and entail separate medicolegal risks. Gamma Knife surgery, particularly with the Perfexion unit, allows for robotics-assisted radiosurgery for a nearly limitless number of brain metastases in one session. However, current professional neurosurgical codes for stereotactic radiosurgery (SRS) allow for reimbursement of up to 5 cranial lesions at one time using primary codes 61796 or 61798 along with add-on codes of 61797 or 61799. Since the SRS code changes in 2009, the reimbursement per lesion up to 5 has been the standard approach utilized by the Centers for Medicare & Medicaid Services and private payers (Dr. R. Patrick Jacobs, chair of the AANS & CNS Coding & Reimbursement Committee, personal communications). The choice of a number like 5 is an arbitrary one that is not relevant to outcome. We hope that the current work and other recent publications lead to expanded recognition of the role of radiosurgery for patients with 5 or more brain metastases and reimbursement commensurate with the effort to treat these challenging patients using single-session radiosurgery.3,5

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Barrow Ruptured Aneurysm Trial: 3-year results

TO THE EDITOR: We would like to elaborate on some of the issues that have been brought forward in the Journal of Neurosurgery following the recent publication of the 3-year Barrow Ruptured Aneurysm Trial (BRAT) results7 (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), as well as the editorial comments and response that followed. The first point we would like to emphasize is that if dialogue on the meaning of trial results in terms of impact on clinical practice is necessary, it would be naïve to believe that everything about ruptured aneurysms can now be settled by argumentation. The ongoing controversy indicates that more hard work is ahead: as proposed by the BRAT team, other trials are needed, and their design

This article contains some figures that are displayed in color online but in black-and-white in the print edition.
should be informed by what we have learned from the International Subarachnoid Aneurysm Trial (ISAT) and BRAT. Concrete efforts in this direction are underway. If each ISAT or BRAT publication is followed by numerous comments and editorials, it is because trials have the power to change medical practice. Although this notion may be distorted to suggest that trials can be designed to convince others, to win arguments or turf battles, we stress that trials must be designed to improve patient outcomes. One way they can achieve this is to provide answers that will inform how we treat future patients. What is less well recognized is that trials can be designed to improve patient outcomes immediately, for the benefit of the actual patients recruited into the trial. We believe this has been shown by BRAT, once the subtleties of this type of trial design are unpacked (see below).

The point we would like to make is difficult to articulate, but its importance is worth the effort: analysis of the differences in design of BRAT and ISAT can help us understand why trials are difficult and uncommon in surgical specialties, even though they are desperately needed. This analysis can shed light on how to design trials that are integrated with patient care in order to ensure that prudent introduction of promising surgical developments and the validation that they actually deliver the good outcomes they promise occur together, in real time.

ISAT was a conventional randomized controlled trial (RCT), while BRAT’s unusual design used a kind of pre-randomization, a device proposed by Zelen that notoriously “saved” a difficult, nonrecruiting breast cancer trial. The trial eventually produced “extraordinarily significant human benefits”; nevertheless, Zelen’s design has ever since remained “ethically suspicious,” for consent-related reasons too intricate to rehearse here. In a previous comment we, perhaps too hastily, carried over a number of scientific and ethical concerns related to the use of Zelen’s design in BRAT; for there are merits to this approach.

Scientifically speaking, whatever is left unquestioned cannot be answered by the data at the end of any trial. In order to be recruited into conventional trials, patients must be eligible for both treatment options. While intentionally narrow selection criteria can endanger generalization of trial results, ISAT was appropriately inclusive by design. The ISAT designers, however, could not control for how participating clinicians determined study “eligibility,” a vague concept that is open to interpretation. It would be unwise, if not unethical, to force clinicians to use a treatment they believe is inappropriate for the case at hand. Yet, the unquestioned beliefs of the clinicians that determine eligibility can endanger generalizability of trial results, if clinicians enroll only patients for whom their own narrow conception of “equipoise” applies (Fig. 1).

BRAT addressed this problem by assigning a treatment modality before clinicians could exclude patients from the study, and thus BRAT captured more subarachnoid hemorrhage (SAH) patients overall. The problem, however, reappears at another level, as patients were crossed over from coiling to clipping (leaving aside the problem of enrolling the SAH patients without aneurysms, which we do not wish to discuss here) (Fig. 1). “To whom do the results of BRAT apply?” also remains an obscure question, because the beliefs of the clinicians that chose to cross patients over, just as the beliefs of the clinicians that chose not to include a patient in ISAT, remain unquestioned.

We have in fact traded a problem with eligibility for a problem of cross-overs, both being related to an apparently legitimate use of clinical judgment. No doubt, some hematomas need to be drained. More frequently, cross-overs in BRAT and nonelegibility for ISAT involved patients with aneurysms thought to be unfavorable for coiling, a judgment that can only be vague, can only be variable from one clinician to another, and can only change in time as proficiency and technique evolve. After all, ISAT was interrupted more than 10 years ago.

The difficult problems here are related to the purported clash between care and research. Because these clinical activities are traditionally separated and understood as having diverging aims, a tension seems to exist between what is the best way to answer a research question (presumably for the benefit of future patients) and what clinicians believe is the best way to care for this or that particular patient. This tension could be appeased if trials were designed and recognized as the way to deliver optimal care in the presence of uncertainty.

If the problem of eligibility is common with conventional randomization, especially in surgical trials, Zelen’s design can help, but the strategy may become self-defeating, as cross-overs increase with pre-randomization. With a greater number of cross-overs, interpretation of the meaning of intent-to-treat and per-treatment results becomes difficult, and we are left with numbers and groups that are vaguely defined and barely projectable to future patients. Interestingly, Zelen’s own calculations indicate that for pre-randomization to be efficient, the proportion of patients having no preference should be greater than the proportion of physicians willing to participate in a conventional RCT.

What we would like to emphasize here is that the design used in BRAT can be conceived as the prudent way to introduce coil embolization in an environment where clip occlusion has always been standard treatment (for the sake of this argument, we assume coiling is yet to be validated, and that clipping is the accepted, standard treatment). In this way, each BRAT patient was given a 50% chance of having the new, promising treatment, and at the same time, given an equal 50% chance of escaping what might be a false promise. In a context where a still-unvalidated treatment option is proposed to replace standard therapy, leaving the coilers free to cross over to standard treatment when they are uncomfortable remains a prudent course of action. Had BRAT shown poor results of coiling, an inappropriate change in practice would have been interrupted early. Of course, nobody knows what would have happened to patients crossed over to clipping had they been treated with coil embolization, but since coiling did lead to better outcomes for patients actually treated with coils, compared to all other groups, it is fair to say that during the trial, BRAT prudently improved outcomes of the patients admitted at the Barrow. This is no small achievement. The important lesson here is that participation in trials can improve patient outcomes immediately, even before the results of the trial are avail-
able for discussion. The best way to achieve this, with pre-randomization or with conventional trials, remains to be seen. In surgical cultures that are typically resistant to conventional trials, the BRAT design may well be the best way to achieve better patient outcomes immediately.

Providing optimal medical care in the presence of uncertainty and providing evidence regarding the best way to care for patients may turn out to be the same thing, simply viewed at different time points: during the trial and then once the trial results are in. Alternative policies, such as widespread and premature adoption of new devices and treatments that can do more harm than good (carotid artery stenting, for example), or conversely, obstinate refusal to conceive of potential replacements for suboptimal standard practices, can only offer inferior care compared to what a patient is offered within a well-designed trial. We must learn to integrate trials into clinical routine to provide optimal care in the presence of uncertainty.

We have learned a lot from ISAT and BRAT. However, much remains uncertain. For patients not included in the original ISAT, or for those crossed over to clipping in BRAT, a trial exists: we suggest participation in ISAT II.1

**Fig. 1.** Comparison of pre-randomization and classical RCT designs.

**Disclosure**

The authors have designed and are investigators for the ISAT II study.

**References**


**Response:** Darsaut and Raymond provide a useful articulation of the different limitations inherently imposed upon ISAT and BRAT by their contrasting study designs. We are grateful for their expansion on this topic, as detailed discussions of important nuances are frequently curtailed as a result of editorial decisions.

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Awake craniotomy

To The Editor: We read the article by Dr. Milian and colleagues2 (Milian M, Luering D, Ploppa A, et al: “Imagine your neighbor mows the lawn”: a pilot study of psychological sequela due to awake craniotomy. Clinical article. J Neurosurg 118:1288–1295, June 2013). Three years ago, we published a paper1 regarding patients’ perceptions of awake craniotomy in this journal, and our findings were quite different. It is unfortunate that Dr. Milian’s literature search failed to turn up our paper. In general, the patients in our study reported a positive experience with awake craniotomy, to the point that they would recommend the procedure to another patient and would be willing to repeat the experience themselves if another operation were necessary. Although most of the patients experienced some anxiety prior to surgery, the overwhelming feeling after the surgery was relief. No patient reported having recurrent nightmares, feeling traumatized by the procedure, or needing psychiatric consultation and treatment.

We think Dr. Milian and colleagues came up with a high rate of psychological sequela because of several factors. The first factor is the patient population, with possible inherent differences in the personalitites of patients from 2 different countries. In general, Canadians have great trust in their health care system and their physicians, and that may contribute to their confidence in a procedure recommended to them and help them get through the whole process of awake craniotomy. The second factor is the technique, both the neurosurgical and anesthetic aspects. The senior author has performed about 2000 awake brain surgeries and has fine-tuned his technique. At the same time, the neuroanesthetists are also very experienced, keeping the patients gently sedated and very comfortable until and after cortical mapping. Also, the diagnosis may be a factor. All of our awake craniotomy patients in the study underwent surgery to remove their brain tumors, and their attention may be so focused on the treatment of their tumors that they did not dwell on the experience of awake surgery anymore. They were more concerned with the disease than the procedure, and surgery was often only one of the many treatment modalities that they had to undergo. Finally, Dr. Milian and colleagues used surveys while we used face-to-face interviews, which may allow a richer pursuit of the information sought. However Dr. Milian and colleagues’ results do nicely demonstrate one of the important weaknesses of qualitative research: the fact that generalizability may sometimes be limited.

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Disclosure
The authors report no conflict of interest.

References

RESPONSE: We regret that in our publication we did not consider the specific paper of Khu and colleagues1 in which they reported on their considerable experience with awake brain surgery procedures. On the other hand, we cited numerous other works2–4 dealing with patients’ satisfaction after awake craniotomy. Awake craniotomy is a procedure that is well tolerated by the majority of patients, and we clearly stated that finding in the discussion section of our manuscript.

However, one must not forget that the fact that most patients tolerate the procedure well (as was the case in our cohort too) is merely a “snap-shot” of the situation. This does not mean at all that psychological sequelae—for example, dreams or memories of the event—cannot occur temporally delayed afterwards, especially since much happens subconsciously. While Khu and colleagues reported on their experiences with patients’ short-term reactions (that is, 1–2 weeks postsurgery), we aimed to investigate possible long-term psychological consequences. We are convinced that the whole setting and operative procedure is always an exceptional and stressful situation for the patient involved, no matter how thorough the preparation of the patient preoperatively, how professional the conduct of the procedure itself, and how good the intraoperative supervision and attendance to the patient may be. Therefore, we do not find it surprising that patients can develop single psychological symptoms after this procedure.

Although the study setting and question of Khu and Bernstein were quite different from ours, their conclusions are not at all contradictory to ours: we do recommend and advocate awake craniotomy in appropriate cases and we are convinced that, with the proper preparation, the procedure can be safely performed to the patients’ benefit. However, we recommend considering possible long-term effects when planning this type of surgery.

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Hypertonic saline

To The Editor: We are highly interested in the clinical article by Eskandari et al. (Eskandari R, Filtz MR, Davis GE, et al: Effective treatment of refractory intracranial hypertension after traumatic brain injury with repeated boluses of 14.6% hypertonic saline. Clinical article. J Neurosurg 119:338–346, August 2013). Head injury–induced refractory intracranial hypertension is an emergent condition in neurocritical care. Eskandari and colleagues conducted a clinical study to identify the effect of hypertonic saline (HTS) on the treatment of intracranial hypertension. They found that the subgroup of patients with head injury–induced intracranial hypertension totally intractable to all other medical treatments can be managed efficiently and safely with frequent boluses of 14.6% HTS instead of a single bolus.

However, they did not perform a side-by-side comparison of HTS with positive control data, such as mannitol or glycerol treatment response. Moreover, the molecular mechanism of the HTS-regulated signaling pathway is very important. Despite these minor limitations, their study pointed out one very important application of HTS. They found that the subgroup of patients with head injury–induced intracranial hypertension totally intractable to all other medical treatments can be managed efficiently and safely with frequent boluses of 14.6% HTS instead of a single bolus.

We are highly interested in the clinical article by Eskandari et al. (Eskandari R, Filtz MR, Davis GE, Hoesch RE: Effective treatment of refractory intracranial hypertension after traumatic brain injury with repeated boluses of 14.6% hypertonic saline. Clinical article. J Neurosurg 119:338–346, August 2013) head injury–induced refractory intracranial hypertension is an emergent condition in neurocritical care. Eskandari and colleagues conducted a clinical study to identify the effect of hypertonic saline (HTS) on the treatment of intracranial hypertension. They found that the subgroup of patients with head injury–induced intracranial hypertension totally intractable to all other medical treatments can be managed efficiently and safely with frequent boluses of 14.6% HTS instead of a single bolus.

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Therefore, we believe that further prospective multicenter trials are warranted to clarify the long-term outcome of head injury–induced intracranial hypertension.

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Disclosure

The authors report no conflict of interest.

Reference


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

![Fig. 1. Schematic representations of the relationship of the supradiaphragmatic craniopharyngiomas (SE [A], intraventricular and extraventricular [B], and intraventricular [C]) with the floor of the third ventricle (dashed). Copyright Juraj Šteňo. Published with permission.]

to a more accurate term, “intraventricular and extraventricular craniopharyngiomas.” We have described in detail the state and location of the structures forming the TVF in all 3 types of supradiaphragmatic craniopharyngiomas.

The intraventricular and extraventricular (IVEV) craniopharyngiomas were in direct contact with the cerebral tissue of the remnants of the TVF, which were displaced around the horizontal circumference (“equator”) of the tumor at the border between its intraventricular and extraventricular portions. The pia mater continued from the atrophied remnants of the TVF and the chiasm down to the basal part of the tumor. We considered it as proof of an intracerebral origin of the tumor growth, which started inside the infundibulum/tuber cinereum as stated by Northfield and Grekhov. Full disruption of the pia along the entire tumor-hypothalamus and the tumor-chiasm junction was seen in only 2 of 18 cases.

The structures of the TVF covering the lower surface of the intraventricular craniopharyngiomas were not completely intact in any of our sectional cases. The central part of the tuber was always atrophied; a small part of the lower pole of the tumor was thus covered by the pia only. Well-preserved brain tissue containing normal-appearing neurons was found in the lateral parts of the tuber and in the undamaged mammillary bodies. In one case a small cystic part of the tumor bulged downward into the retrostellar region below the level of the TVF. We considered it to be a transitional form overlapping with the IVEV craniopharyngiomas. Later on we classified such tumors as IVEV craniopharyngiomas. We agree with Pascual et al. that a majority of the intraventricular craniopharyngiomas described in the literature should be reclassified as IVEV (“not strictly intraventricular”). In our clinical series we encountered a single patient with an intraventricular craniopharyngioma. Our experience shows that there is a gradual transition of the extent of destruction of the TVF between a purely intraventricular tumor covered from below by the TVF with only minimal disruption of its subependymal layer and a typical IVEV craniopharyngioma with the remnants of the TVF displaced around its equator. For instance, in some patients with IVEV tumors we preserved the infundibulum covering the basal pole of the tumor that was not recognized on preoperative MR images (Fig. 2). There seems to be a proportional dependence: the more extensively the tumor destroys the TVF, the more extensive is its adherence to the ventricular walls. The intraventricular tumors were always attached to the structures forming the TVF and only occasionally adhered to the basal parts of the lateral walls (Fig. 3). The IVEV craniopharyngiomas always extensively adhered to both the remnants of the TVF and to the lateral walls of the ventricle. The tumor parenchyma, its gliotic capsule, and surrounding brain tissue of the diencephalon often formed one layer of tissue (Fig. 2). Both, the extent of destruction of the TVF and the extent of adherence of the tumor to the diencephalon, were depicted in our schemes (Fig. 1). Similar tumor-hypothalamic relationships were also discovered later by others.

Topographic features of the craniopharyngiomas involving the third ventricle, as described above, were later adopted by Pascual et al. They termed the intraventricular craniopharyngiomas as “strictly intraventricular.” The tumors identical with our intra-extraventricular or IVEV craniopharyngiomas they classified as “non-strictly intraventricular” or “not strictly intraventricular.” The SE craniopharyngiomas were named “pseudo-intraventricular.” The authors recognized also the fourth topographical group of the supradiaphragmatic tumors, the “secondarily intraventricular” craniopharyngiomas. According to the authors such a tumor develops below the TVF within the suprasellar compartment (usually originating at the upper stalk) that eventually invades the third ventricle after breaking through its floor and it becomes an extra- and intraventricular tumor. Among more than 200 craniopharyngiomas in our morphological and clinical series we could assume such a pathogenesis in 5 IVEV tumors. In our study on supradiaphragmatic craniopharyngiomas correlating the morphological, radiological, and operative findings, we preoperatively assumed that 18 (of 44) tumors were extraventricular. However, during surgery the superiorly displaced TVF was found to be defective in 3 patients; the upper pole of the tumor was located inside the ventricular cavity. We found an additional 2 cases in the morphological series where the pia mater was disrupted at the junction of the
tumor and the remnants of the TVF. The continuation of the pia to the tumor surface could not be traced. The first 3 tumors could cause disruption of the thinned-out TVF at the later stages, and the latter 2 tumors could break into the third ventricular cavity at an early stage of their growth. However, none of the tumors was constricted at the level of the TVF as depicted in the scheme of the secondarily intraventricular tumors of Pascual et al.\(^8\) (their Table 3). The strangulation grooves on the surface of the tumor were caused by cranial nerves and/or the arteries. In fact, the pathological anatomical specimen (their Fig. 3D3) presented as a secondarily intraventricular type of tumor does not substantially differ from the not strictly intraventricular tumor (their Fig. 3B3); both displayed the same topographical features as we described in the group of IVEV craniopharyngiomas.\(^12,14\) From a clinical point of view it is important that in both (that is, the not strictly intraventricular and the secondarily intraventricular craniopharyngiomas) the TVF is defective. Consequently all these tumors may be attacked by both the transventricular (transcallosal and trans–lamina terminalis) and the extraxial approaches as we reported in patients with IVEV craniopharyngiomas.\(^14\) The surgical case (their Fig. 3D1 and D2) was resected via combined transcallosal, trans–lamina terminalis, and extraxial approaches.\(^15\) Moreover, the values of the mammillary body angles measured by the authors showed the highest variability in the group of the secondarily intraventricular craniopharyngiomas. Therefore, we do not consider distinguishing a separate topographical group of secondarily intraventricular craniopharyngiomas well grounded from clinical reasons.

We agree with Pascual et al.\(^8\) that the hypothalamic structures cannot be detected easily on preoperative MR images. Therefore, we greatly appreciate their contribution adding to the possibilities of preoperative localization of the TVF in relation to suprapiaphragmatic craniopharyngiomas. It is of utmost importance to distinguish the SE craniopharyngiomas from the other suprapiaphrag-
matic tumors. The SE craniopharyngiomas are separated from the hypothalamus by the pia mater (Fig. 4). Morphologically they are thus clearly distinguished from both the intraventricular and from the IVEV craniopharyngiomas that are in direct contact with the cerebral tissue.12 The great majority of SE craniopharyngiomas, especially in pediatric patients, can therefore be safely separated from the TVF located at their upper surface.10,13,14 However, some SE craniopharyngiomas may firmly adhere to the pia and its vessels supplying the TVF to a degree, precluding safe tumor removal.11 It may be the consequence of the original growth of the tumor at the upper part of the pituitary stalk among the arachnoid trabeculae as reported by Qi et al.,9 although the toxic nature of the content of the tumor cyst may also play a role.

In our study14 performed with similar intentions as those of Pascual et al.8 we found 2 factors that allow distinguishing the SE tumors from IVEV and intraventricular craniopharyngiomas: the presence or absence of hydrocephalus and the tumor-chiasm relationship.

Hydrocephalus was found in 22 of 28 IVEV tumors, while it was absent in 14 of 15 SE craniopharyngiomas including the tumors of a giant size apparently occluding the entire chamber of the third ventricle. Pascual et al.8 also found very low hydrocephalus rates in the “pseudointraventricular” tumors in comparison with the “strict” and “non-strict” intraventricular tumors.

The tumor-chiasm relationship differed depending on the relationship of the tumor with the hypothalamus. Suprasellar extraventricular craniopharyngiomas originating from the pituitary stalk grew below the chiasm, displaced it superiorly, and often extended in front of it. In one-third of the patients the prechiasmatic part of the SE tumor represented at least one-third of the entire lesion. The IVEV craniopharyngiomas originating in the infundibulum/tuber cinereum at the posterior angle of the chiasm pushed it anteriorly. The premorbid length of the optic nerves also determined the resulting position of the chiasm in relation to the tumor. In patients with shorter optic nerves the chiasm was located on the anterior surface of the IVEV tumor. A small part of it may extend below the chiasm into the chiasmatic cistern, where it could be reached via the prechiasmatic space. Even in these cases the IVEV tumor remained retrochiasmatic (Fig 5). In patients in whom the chiasm could not be seen on the MR images, it could be detected indirectly according to the position of the anterior communicating artery (ACoA) lying just above the chiasm. In IVEV craniopharyngiomas the ACoA was always located on the anterior surface of the tumor. In patients with large and giant SE tumors, the ACoA caused strangulation of the chiasm and the tumor, showing thus the border between the prechiasmatic and retrochiasmatic portions of the tumor.12,14 On the basis of our results, we assume that the analysis of a predictive significance of the tumor-chiasm and the tumor-ACoA relationships would have added to the already high practical value of the paper of Pascual et al.8
Our experience shows that the preinfundibular and the retroinfundibular craniopharyngiomas according to the classification of Kassam et al., including their type IIIa tumors growing toward the third ventricle may all be extraventricular and may be resectable with an excellent surgical outcome. Moreover, in our morphological series we observed a case of SE tumor displacing the pituitary stalk laterally; such a tumor may be classified as “parainfundibular.” Regardless, the manifold relationship of the above-listed tumors to the pituitary stalk all have common topographical feature, which is the location above the sellar diaphragm and outside the third ventricle. The transinfundibular craniopharyngiomas of Kassam et al. have a more intimate relationship with the hypothalamus corresponding to that in our IVEV craniopharyngiomas.

We can conclude that the craniopharyngioma-hypothalamus relationship is crucial as it determines if the tumor is safely resectable. The relationships of the tumor with the optic chiasm and the pituitary stalk affect primarily surgical accessibility of the tumor. Our results also showed that the relationships of craniopharyngiomas with these structures are at least partially determined by the tumor-hypothalamus relationship.

**Disclosure**

The authors report no conflict of interest.

**References**


**RESPONSE**

We greatly appreciate the thoughtful and scholarly letter from Professor Juraj Šteňo and the members of his Department of Neurosurgery in Bratislava, Slovakia, one of the leading groups in the surgical treatment of craniopharyngiomas worldwide. At the outset, we wish to remark how honored we are for the attention Šteňo and his colleagues paid to our recently published study on craniopharyngiomas. Professor Šteňo’s surgical experience and research on craniopharyngiomas represent one of the cutting-edge efforts to understand these baffling, challenging lesions. In fact, our initial interest in craniopharyngiomas was triggered after reading his masterpiece study on the topographical relationships of craniopharyngiomas, published in 1985. The major, fundamental finding of his study was to provide definitive evidence for a hypothalamic-intraventricular primary location of most craniopharyngiomas in adult patients, a concept contrary to the conventional “suprasellar” position assigned to these tumors. By focusing the experts’ attention on the craniopharyngioma adherence to the hypothalamus, Šteňo picked up the thread of the narrative initiated by Jacob Erdheim in 1904, who noticed that the infundibulum and tuber cinereum constituted the primary location of “hypophysengangsgeschwülste,” or hypophyseal duct tumors. During the first half of the 20th century major experts on the treatment of craniopharyngiomas, such as Norman Dott, Percival Bailey, William Northfield, and Edgar Khan, warned about the intimate functional and anatomical relationships between craniopharyngiomas and the hypothalamus. Nevertheless, the little emphasis given to macroscopic pathological evidence, in addition to the lack of accuracy of diagnostic methods used before MRI, influenced the generalization for the concept of craniopharyngiomas as tumors with a suprasellar topography. Šteňo’s findings allowed experts to reconsider such an inaccurate concept, shifting the spotlight from the suprasellar area to the hypothalamus and third ventricle as the principal sites for craniopharyngiomas. In fact, his topographical classification has been quoted and described in detail in all our studies. Šteňo’s classification scheme for craniopharyngiomas defines the IVEV category as the one in which part of the lesion expands within the third ventricle and part...
outside the ventricle. This type of craniopharyngioma showed the most severe disruption of the third ventricle floor (TVF) and the tightest adherence to the hypothal- amus. In contrast, our classification scheme for craniopharyngiomas involving the third ventricle was initially designed with the aim to precisely differentiate between those lesions truly developing within the third ventricle (strictly intraventricular craniopharyngiomas) and the much more prevalent group of craniopharyngiomas developing either at the level of the proper TVF (not strictly intraventricular craniopharyngiomas) or below the third ventricle. Preoperative differentiation between strictly and not strictly intraventricular craniopharyngiomas is of paramount importance for neurosurgeons, as the subpial, intraneural origin of the latter group determines their tight adherence to the hypothalamus. From a surgical perspective, both types of craniopharyngiomas can be considered as primary intraventricular tumors, because they exclusively or largely develop within the third ventricle and a trans–third ventricle approach is required to properly remove the tumor from its attachment to the TVF.

Morphological features of not strictly intraventricular craniopharyngiomas (also known as infundibulotuberal craniopharyngiomas) are the result of the primary growth of the mass into the third ventricle cavity. These lesions do not show a symmetrical growth within and outside the third ventricle, yet they expand predominantly into the third ventricle chamber. In a considerable number of cases, a patent suprasellar cistern and a partially or wholly intact pituitary stalk can be observed beneath the tumor on sagittal and coronal MR images. More to the point, most not strictly intraventricular craniopharyngiomas do not involve the sella turcica. As the tumor progresses, it gradually replaces the TVF, leaving a circumferential, wide rim of attachment to the remnants of the TVF. The group of not strictly intraventricular craniopharyngiomas represents only a part of the lesions included within the IVEV category defined by Šteňo and colleagues. A second major category of craniopharyngiomas causing true invasion of the third ventricle can be considered, one formed by those tumors developing originally within the sellar or suprasellar compartments that protrude into the third ventricle as they enlarge. Erdheim defined 2 preferential anatomical points for the origin of craniopharyngeal duct tumors along the hypothalamos-pituitary axis, one at the upper end of the pars tuberalis, just at the junction of the infundibulum with the optic chiasm, and the other at the junction of the pituitary stalk and the dorsal surface of the pituitary gland. Craniopharyngiomas with an infradiaphragmatic origin at the hypophysial-stalk junction level represent most sellar-suprasellar lesions largely expanding along the suprasellar arachnoid compartments. Interestingly, these lesions with a primary extraventricular topography are observed more frequently among children and young patients, show an adamantinomatous histology in almost all cases, and display a typical multilobular morphology with solid-cystic tumor extensions filling the different compartments of the basal arachnoid cisterns. Large cysts from craniopharyngiomas with an original extraventricular position expanding upward against the base of the brain usually occupy the space of the third ventricle after folding the TVF inward. Other tumors actually invade the third ventricle after breaking through the thinnest midline area of the third ventricle floor. We consider the term “secondary intraventricular craniopharyngiomas” to differentiate the latter subgroup of lesions. Introducing the secondary intraventricular category brings in a dynamic, time course factor to the topographical classification of craniopharyngiomas, as the occupation of the third ventricle chamber does not occur initially but at later stages of craniopharyngioma development. In this sense, the terms “not strictly intraventricular” and “secondary intraventricular” differ from the topographical categories defined by Šteňo et al., which describe the final anatomical relationships between the tumor and the TVF.

In their letter, Šteňo et al. point out the gross morphological similarities they observed between the example lesions displayed in Fig. 3 of our paper, corresponding to the not strictly intraventricular and the secondary intraventricular craniopharyngioma types. Actually, some important differential characteristics should be noted between these two examples, both on MRI and on macroscopic brain sections. Not strictly intraventricular craniopharyngiomas are characterized by their round, smooth shape, with a basal solid nodule growing at the level of the TVF, above a patent suprasellar cistern, and a unicellular cyst filling the third ventricle. In this type of craniopharyngioma the sellar compartment is tumor free, the lower portion of the pituitary stalk remains intact beneath the tumor, and the mammillary bodies are observed to be located at the same level as the bottom of the lesions. In contrast, the secondary intraventricular examples correspond to elliptical solid-cystic lesions extending from the sellar compartment to the third ventricle, with their basal solid portions grossly infiltrating or enveloping the entire trajectory of the no longer recognizable pituitary stalk. In these craniopharyngiomas the mammillary bodies are found at the level of the “equator” or central part of the lesion. Specific morphological features of not strictly intraventricular craniopharyngiomas and secondary intraventricular craniopharyngiomas were investigated for the cases included in our paper (n = 81), with the aim of identifying objective MRI signs to help neurosurgeons make an accurate differential diagnosis between the types (present Table 1). Major differential characteristics for the secondary intraventricular category were a marked predominance of solid-cystic multilobulation (67%), extension of the lesion along the basal arachnoid cisterns (47%), and enveloping/invasion of the entire pituitary stalk length (90%).

We agree with Šteňo and colleagues’ claim that tumor constriction caused by the TVF around the central portion or equator of the tumor is not normally observed in craniopharyngiomas showing an IVEV topography. The illustrative coronal scheme of the secondary intraventricular category displayed in Table 3 in our paper was designed for didactic purposes to highlight the invasion of the third ventricle by the upper extension of a craniopharyngioma with an original sellar-suprasellar location. Nevertheless, in our thorough review of craniopharyngiomas invading the third ventricle that were reported in the literature, we have been able to find examples of secondary intraventricular
introduced the differentiation between a primary versus a secondary intraventricular extension of the lesion. In the second category he included suprasellar craniopharyngiomas, which had invaded the third ventricle through any defect in the ventricle floor. A similar concept is considered in the classification schemes by Gaya Yaşargil and by Michael Apuzzo for the group of extra-/intraventricular craniopharyngiomas. For their part, Tomita et al. differentiated between the sellar-suprasellar type (37%) and the sellar-intraventricular type (40%) in their pediatric series of craniopharyngiomas. In the latter category the authors included those lesions extending from the sellar compartment upward into the third ventricle chamber, in contrast to the former type constituted by lesions limited to the sellar and suprasellar compartments that had pushed the TVF upward. The series of 284 craniopharyngiomas operated on by Shi et al., formed predominantly of adult patients, was classified into the “superior” type—equivalent to a primary intraventricular development—and the “inferior” type, grouping the lesions with a primary origin below the third ventricle. Within the latter category, 92 cases (32%) extended from the superior sella upward into the third ventricle, corresponding to our secondary intraventricular category. Finally, in the comprehensive analysis of the meningeal relationships of craniopharyngiomas recently provided by the group of Qi et al., 2 major types of secondary involvement of the third ventricle were identified: 1) extra-intraventricular craniopharyngiomas, presumably developing within the trabecular portion of the arachnoid covering the infundibulum, which had extended through the third ventricle floor (5% of cases); and 2) transinfundibular lesions, extending from an infradiaphragmatic location along the intrarachnoidal portion of the pituitary stalk into the third ventricle (2% of craniopharyngiomas). These lesions were differentiated from the much more prevalent group of subarachnoidal (infundibulotuberal) craniopharyngiomas, developing primarily within the TVF.

An accurate MRI topographical diagnosis of secondary intraventricular craniopharyngiomas could not be made merely with the measurement of the mammillary angle in our study. The major reason was the high variability observed in both the direction and degree of displacement of the mammillary bodies within this topographical category. Whereas some extra-intraventricular lesions had pushed the TVF upward before invading the ventricle, causing a dorsal displacement of the mammillary bodies far from the brainstem, others had expanded preferentially within the floor pushing the mammillary bodies backward against the brainstem. Consequently, extremely acute and obtuse values for the mammillary angle can be measured within this category. Other signs must be used to establish the diagnosis, such as the multilobular shape of the mass, its sellar occupation, the pituitary stalk envelopment, and/or their extension through the basal cisterns.

The differentiation of an intra-extraventricular topography for a majority of craniopharyngiomas, especially among adult patients, is a valid, useful concept warning neurosurgeons about the lesions’ expected tight adherence to the hypothalamus. All neurosurgeons should recognize

craniopharyngiomas showing such a central tumor constriction at the level of the remnants of the TVF on midsagittal and coronal brain sections (see the example of the case displayed in Northfield’s textbook). In the series of 130 craniopharyngiomas included in our study, a tumor central constriction was identified on preoperative MR images in 23% of secondary IV lesions.9

The secondary intraventricular category of craniopharyngiomas is supported by multiple pathological, neuroradiological, and surgical findings from the literature. After analyzing the macroscopic topographical relationships of 185 craniopharyngiomas, Klaus J. Zülch

| TABLE 1: Differential characteristics between the not strictly (infundibulotuberal) and the secondary intraventricular craniopharyngioma topographical categories* |
|-----------------|-----------------|-----------------|
| CP Characteristics | Not Strictly IV CPs (n = 51) | Secondary IV CPs (n = 30) |
| age (yrs)         |                  |                  |
| children (<18)    | 44%              | 60%              |
| adults (>18)      | 56%              | 40%              |
| shape             |                  |                  |
| round             | 40%              | 0%               |
| elliptical        | 57%              | 33%              |
| multilobulated    | 3%               | 67%              |
| consistency       |                  |                  |
| pure solid        | 27%              | 6%               |
| cystic-basal solid| 8%               | 16%              |
| pure cystic       | 41%              | 33%              |
| mixed solid-cystic| 23%              | 43%              |
| sella turcica involvement | |                  |
| invaded by tumor  | 17%              | 47%              |
| tumor free        | 83%              | 53%              |
| pituitary stalk involvement | |                  |
| whole stalk infiltrated/invaded | 47% | 90% |
| partial/whole stalk length intact | 53% | 10% |
| suprasellar cistern involvement | |                  |
| tumor free        | 12%              | 0%               |
| partially occupied| 55%              | 27%              |
| entirely occupied  | 37%              | 63%              |
| CP extensions into basal cisterns | |                  |
| present           | 18%              | 47%              |
| absent            | 82%              | 53%              |
| pituitary gland   |                  |                  |
| visibly intact    | 88%              | 60%              |
| compressed/invaded by tumor | 12% | 40% |
| tumor constriction by the TVF | |                  |
| visible           | 2%               | 23%              |
| lacking           | 98%              | 77%              |
| mammillary angle (preop) | |                  |
| acute (<90°)      | 100%             | 77%              |
| obtuse (>90°)     | 0%               | 23%              |

* CP = craniopharyngioma.
this concept as a fundamental contribution by Šteňo. The group of craniopharyngiomas developing primarily within the infundibulotuberal area of the TVF constitutes the majority of IVEV craniopharyngiomas. However, craniopharyngiomas originating at the sellar or suprasellar compartment may eventually invade the third ventricle. This latter category of secondary intraventricular craniopharyngiomas should be identified preoperatively to predict hypothalamic invasion and plan the appropriate surgical procedure accordingly.

References


Posterior inferior cerebellar artery aneurysms

To The Editor: We read with interest the article by Chalouhi et al.3 (Chalouhi N, Jabbour P, Starke RM, et al: Endovascular treatment of proximal and distal posterior inferior cerebellar artery aneurysms. Clinical article. J Neurosurg 118:991–999, May 2013) in which the authors preferentially offered endovascular therapy to patients with posterior inferior cerebellar artery (PICA) aneurysms and acquired experience with 76 patients.3 Treatment consisted of selective aneurysm coiling for 47 proximal and 13 distal PICA aneurysms and parent vessel occlusion/trapping for 5 proximal and 6 distal PICA aneurysms. Treatment failed in 5 patients (3.7%) and was complicated in 9 patients (12.7%) by 6 infarcts (8.5%) and 3 intraprocedural ruptures (4.2%). Procedure-related morbidity was 2.8% (2 patients), and in-hospital mortality was 7.0% (4 patients). Complete aneurysm occlusion was achieved in 45 patients (63.4%), with one subacute rerupture (1.4%) and an overall recurrence rate of 22.9% (11 patients). Nine patients (18.8%) required retreatment. We commend the authors for their excellent work and favorable outcomes in 82% of the patients, but we think that these results do not support endovascular therapy as a “reasonable first-line option” for PICA aneurysms. The combination of endovascular treatment failures, complications, incomplete aneurysm occlusions, and recurrences/retratements continue to demonstrate that surgery remains a competitive treatment option, if not a superior one.

We agree that PICA aneurysms are challenging from a surgical perspective because of their intimate relationship to the medulla and lower cranial nerves. However, surgical morbidity is misrepresented in this report. The far lateral approach provides excellent exposure of the parent vertebral artery, early proximal control of the aneurysm, and adequate room in the postcondylectomy corridor to visualize most PICA aneurysms. The results of Horowitz et al.5 in 34 patients cited in their paper are not representative of surgical therapy. Our group documented morbidity and mortality rates of 2.1% (1 patient) and 0%, respectively, and good outcomes (Glasgow Outcome Scale Score 5 and 4) in 77.3% of patients in a review of 44 patients with 47 PICA aneurysms, which were treated with direct clipping in 61.7% and occlusion/bypass in 14.9%.6 In a subsequent report on 70 patients with 71 PICA aneurysms, we defined anatomical triangles that allow safe surgical exposure between the lower cranial nerves, with no instances of mortality, 2 patients with permanent neurological morbidity, 1 patient with permanent cranial nerve morbidity, and 2 patients with transient neurological morbidity.7 There
have been no rehemorrhages and only one retreatment for recurrence in our experience. Based on these results, we conclude that the PICA aneurysm is the best example of a posterior circulation aneurysm for which microsurgery should continue to play a primary role.

A prevailing attitude among the endovascular community is that the PICA is expendable with minimal morbidity. This attitude is expressed in the authors’ paper with comments like “trapping of the PICA causes only minimal morbidity,” with anticipated infarcts in “only 36.4% of cases” that were “remarkably well tolerated.” We disagree with a deconstructive approach, particularly when PICA bypass options are so good. We consider PICA occlusion to be a significant complication, and although cerebellar infarcts may be tolerable in some cases, more often they cause secondary deterioration from edema and brainstem compression and require urgent decompressive craniectomy. One of our reported permanent morbidities was from PICA occlusion with this course. We favor a constructive approach that preserves the PICA with direct clipping or replaces flow with bypass when sacrificed.

We have described in our intracranial-intracranial (IC-IC) bypass experience the various options for PICA revascularization, including PICA-PICA bypass, PICA reimplantation, PICA reanastomosis, and interposition grafts that use the vertebral artery as a donor. The cisterna magna is a favorable working space to perform these bypasses, and our results have demonstrated high patency rates and low stroke rates. Distal aneurysms are particularly amenable to a constructive approach, and in our experience with 29 distal PICA aneurysms, we performed bypasses in 7 patients. We were surprised to see that bypass surgery was not used at all in this experience, and the fact that 4 patients suffered cerebellar infarctions suggests that assessments of collateral circulation are unreliable or that bypasses were not performed aggressively enough. The authors demonstrated the difficulties in treating distal PICA aneurysms endovascularly (including the small caliber, tortuosity, and angulations of the parent artery, which preclude coiling), but we would argue that trapping/bypass, rather than deliberate PICA occlusion, should be the next option when endovascular coiling fails.

Finally, the rate of complete aneurysm occlusion in their report was 63%, or 59% when the 5 patients in whom the endovascular treatment failed are included, and 19% of patients required retreatment with associated intra-procedural risks and mounting costs. With a short mean follow-up (17 months), rates of recurrence, retreatment, and rehemorrhage will only increase, as they did with the International Subarachnoid Aneurysm Trial (ISAT) and Barrow Ruptured Aneurysm Trial (BRAT) in long-term follow-up. In contrast, microsurgery for PICA aneurysms is highly effective, with complete occlusion rates over 97%. Therefore, even though PICA aneurysms reside in the posterior circulation, we think that they remain a microsurgical aneurysm, and this option should continue to be offered to patients with both proximal and distal lesions in centers experienced with complex clipping and intracranial bypass techniques.

**Disclosure**

The authors report no conflict of interest.

**References**


**Response:** We thank the authors for their interest in our article and for dedicating a letter to remind neurosurgeons and interventionists of the value of microsurgical techniques in the treatment of posterior circulation aneurysms. All senior authors of our paper are trained in both microneurosurgery and endovascular therapy and frequently use both therapeutic modalities. Indeed, we agree that microsurgery should continue to be offered alongside endovascular therapy to patients with intracranial aneurysms, including PICA aneurysms. In our paper, we reviewed the nuances and outcomes of patients treated with endovascular therapy, but we did not include a large number of patients with PICA aneurysms treated with microsurgery at our institution. However, Level I
evidence from randomized controlled trials should not be overlooked. The ISAT has produced convincing evidence that endovascular therapy is a viable treatment option for a large number of ruptured intracranial aneurysms, especially in the posterior circulation where microsurgery can be challenging. Today, posterior circulation aneurysms, including PICA aneurysms, are primarily managed with endovascular means in many neurovascular centers.

The authors have disagreed with a deconstructive approach to the PICA in favor of a constructive approach. They state that cerebellar infarcts developed in 4 patients in our study, but they fail to mention that none of them had permanent sequelae. Although we also frequently use cerebral bypass surgery for complex PICA aneurysms, we believe that in carefully selected patients endovascular trapping of the PICA can be safely undertaken with minimal morbidity. Authors of several other studies detailed in our paper have also come to this conclusion.

Our study was not designed to determine the best treatment option for PICA aneurysms. However, microsurgery for these lesions can be associated with significant morbidity and mortality. In 2 articles published in Neurosurgery, microsurgical treatment of PICA aneurysms resulted in neurological sequelae and postoperative lower cranial nerve palsies in 68% and 48% of patients, respectively. Moreover, comparative series have consistently shown higher morbidity rates with microsurgery than endovascular therapy. While favorable results are possible with microsurgery, there is a solid body of evidence supporting the excellent safety profile of endovascular therapy for PICA aneurysms. Thus, we stand by our comments that endovascular therapy is a reasonable first-line option for PICA aneurysms, especially for proximal lesions. For patients with distal aneurysms, as summarized in our paper, we believe that “because surgical treatment is usually straightforward and can be undertaken with little morbidity in these aneurysms, we believe that microsurgery remains an equally effective and valuable option in this subset of patients.” Recently, however, we have found that Onyx occlusion of the PICA at the level of the aneurysm is an excellent means of achieving obliteration of distal aneurysms. Our experience with this technique has yielded minimal periprocedural morbidity with excellent angiographic outcomes. At our institution, Onyx occlusion of the PICA at the level of the aneurysm has become an excellent option for many distally located PICA aneurysms.

Finally, the best technique for treating an aneurysm is the one that will produce the best result for a given patient and is dependent upon many factors, including the expertise of the treating team. Clearly, Dr. Lawton and his team have superb expertise in the management of PICA aneurysms and have contributed to our understanding of these lesions and their microsurgical management. We have described our experience in the endovascular treatment of these lesions, which has produced satisfactory results overall. We do agree that microsurgical management of these aneurysms with or without bypass remains an option, which we continue to offer to our patients. Management should always be tailored to the individual patient, taking into consideration all available data (patient, lesion, and treating team) using whatever treatment modality (or combinations thereof) necessary to achieve the best possible result.

### References


Molecular mechanism of hearing loss


Intratumoral hemorrhage is a common pathological presentation in tumors. The posthemorrhagic healing process is accompanied by fibrosis, which leads to scar contracture affecting nerves, vessels, or surrounding parenchyma. Sughrue et al. observed microhemorrhage and fibrosis within vestibular schwannomas. In a multivariate analysis of paraffin-embedded tissue sections, they found
that extensive intratumoral microhemorrhage, or fibrosis, was statistically associated with poor hearing outcome.

Moreover, their conclusion is based on the observation of H & E staining and semiquantitative analysis of extensive fibrosis and microhemorrhage. These methods are widely used in traditional pathological quantitative calculation and are highly reliable through surgery-obtained specimen verification. Furthermore, transforming growth factor-β (TGF-β) plays a major role in the pathogenesis of fibrosis, and it is expressed in vestibular schwannomas. Therefore, it would be of great interest to quantitatively analyze the amount of TGF-β by Western blot analysis or ELISA in the human vestibular schwannoma samples obtained by Sughrue et al.

Their study has established a milestone in the possible mechanism of microhemorrhage, extensive fibrosis, and hearing status. It is critically important to dissect the upstream molecular mechanism in future studies to provide a better understanding of the pathogenesis of hearing loss to improve the hearing outcome in patients with vestibular schwannoma.

**References**


**Disclosure**

The authors report no conflict of interest.

**Acinetobacter baumannii**

To The Editor: We would like to make a comment on an article by Guinard Vives et al. (Guinard Vives CH, Monsalve Duarte GA, Valderrama Beltrán S, et al: Brain abscess caused by multidrug-resistant Acinetobacter baumannii. Case report. J Neurosurg 111:306–310, August 2009).

The importance of Acinetobacter baumannii CNS infections has increased recently, especially since the Iraqi War. The treatment of these infections is not easy due to the inherent multidrug resistance of this A. baumannii. The relevant bibliography is well presented in the article by Guinard Vives et al.

Even as we are aware of the importance of regional differences, we want to present our experience with the use of intrathecal colistin in such infections.

We have recently encountered many cases of A. baumannii CNS infections, mainly ventriculitis, treated successfully with colistin administered intravenously and intrathecially, in combination with other antibiotics, such as tigecycline and meropenem.

Our main conclusions are that the use of colistin is important in the treatment of such infections. Colistin dosage regimens used to treat these critically ill adult patients were associated with suboptimal C_max/MIC ratios (maximum serum antimicrobial concentration/minimum inhibition concentration) for many strains of gram-negative bacilli currently reported as sensitive. The concomitant use of intrathecal colistin is important, because otherwise the low level of penetration (5%) suggests inadequate bactericidal colistin concentrations in the CSF. In the particular case of the abscess, irrigation of its cavity with colistin could be attempted. Concomitant systematic use of other antibiotics is frequently necessary.

We believe that such a treatment regimen can decrease the mortality rate associated with A. baumannii CNS infections.

**Disclosure**

The authors report no conflict of interest.

**References**


**Disclosure**

The authors report no conflict of interest.

**References**


**Disclosure**

The authors report no conflict of interest.
Cranectomy

To The Editor: We have read with great interest the paper published by Oladunjoye et al. (Oladunjoye AO, Schrot RJ, Zwienenberg-Lee M, et al: Decompressive cranietomy using gelatin film and future bone flap replacement. Technical note. J Neurosurg 118:776–782, April 2013). The authors report their nice experience with Gelfilm (gelatin film; Pharmacia and Upjohn) as a barrier over the dural layer in craniectomy to prevent scars in subsequent cranioplasty.

This work is very interesting because the repositioning of bone or synthetic prosthesis for cranioplasty can be a formidable operation, with complications reaching more that 23%. When severe adhesion becomes established under subcutaneous tissue and dura mater, new dural lacerations are frequent, and CSF fistula and infection are major complications. If cranioplasty became a simple procedure with a low rate of expected complications, replacing the calvaria after decompressive craniotomy for trauma, stroke, secondary infection, or other reasons would probably be performed more frequently.

According to this paper the simple addition of a barrier tissue can achieve this objective, and the authors report a low incidence of complications and easy technical development. We absolutely agree with this concept. These patients were treated relatively soon; at a median of 54 days in those with infections related to delayed cranioplasty.

For years we have used different barriers to prevent scars for this indication and our impressions are similar. But we have not seen differences based on the barrier implanted: caprolactone/lactide film; 2 layers of pure equine collagen with one flat side to the brain surface and the other to the galeal plane (Fig. 1); or gelatin film.

The time between craniectomy and cranioplasty is the subject of controversy; some groups consider that early interventions are ideal and others show complications and risks growing exponentially with time. In fact, probably the major reason in the past for not offering cranioplasty in most cases was the negative balance for complications in several groups. Unlike the work of Oladunjoye, our group performed procedures at a median of 150 days, but neither problem was encountered at surgery. In all cases a loose connective layer, similar to that seen at the elevation of the periosteum plane, was used to develop a new epidural space. It was unnecessary to remove any tissue, and the prosthesis or preserved bone was easily implanted, including those implants made under microvascular-free flaps (Fig. 2).

Finally, the authors propose to include the protection of dural space against adhesions as an indication for a commercial product (Gelfilm). However, we think that this assertion warrants a clinical assay and more evidence than was presented in only one nonrandomized study.

In conclusion, the use of a nonadherent barrier when craniectomy is performed is helpful, and probably will convert a very complex surgery such as cranioplasty into an easier procedure. The type of barrier probably will be less important.

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Disclosure

The authors report no conflict of interest.

References


Response: We thank Dr. Márquez-Rivas and his colleagues for their thoughtful comments on our manuscript.
As they eloquently mention, complication rates following decompressive craniectomy can be surprisingly high and are often due, in part, to the technical challenges of performing a safe bone flap replacement operation. Our standard approach to decompressive craniectomy includes a multilayered onlay repair of the epidural space to prevent adhesion formation between intracranial contents and the overlying musculocutaneous flap. We have found this strategy to be simple and effective—it does not increase operating time, blood loss, or infection rates, and subsequent bone flap replacement surgery is technically simpler to perform because the musculocutaneous flap does not adhere to underlying tissues (brain and dura mater). This modified technique has the potential of improving clinical outcomes in patients who undergo decompressive craniectomy for traumatic brain injury, stroke, and subarachnoid hemorrhage; of course, one cannot claim that this technique is superior without a randomized clinical study.

We agree with Dr. Márquez-Rivas and his colleagues that the advantages we found using the gelatin film barrier (Gelfilm) may also be achieved using other implant types. Other commercially available implant materials may have similar benefits in decompressive craniectomy surgery, so long as they maintain their nonadhesive properties and structural integrity for the time period between craniectomy and subsequent bone flap replacement surgery, and do not have characteristics that may promote infection, immune response, or other potential complications. Because Gelfilm is a nonporous implant that is commonly used in other surgical applications to prevent adhesion formation, we believe it is an ideal candidate for decompressive craniectomy.

As Dr. Márquez-Rivas and his colleagues discuss, the timing of bone flap replacement surgery remains a topic of some debate. Our institutional experience with early (≤30 days) bone flap replacement surgery has been consistent with data reported from other groups, demonstrating lower complication rates and improved neurological outcomes.1–4 There are many reasons why decompressive craniectomy may improve patient outcomes, including earlier participation in aggressive rehabilitation therapy and improvement in regional cerebral blood flow.5 Our experience with the multilayered repair suggests that another advantage of early surgery may be that it is technically simpler and safer because it allows less time for adhesions to form.

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