Neurosurgical forum
Letters to the editor

Traumatic brain injury and hypothermia

To the Editor: We read with great interest the article by Harris et al. (Harris OA, Muh CR, Surles MC, et al: Discrete cerebral hypothermia in the management of traumatic brain injury: a randomized controlled trial. Clinical article. J Neurosurg 110:1256–1264, June 2009). We congratulate the authors for their efforts. Although modeled after our study published in the Journal of Neurosurgery in 2004,1 this study demonstrated, in sharp contrast to our conclusions, the lack of true intracranial hypothermia using a commercially available cooling cap by CoolSystem, Inc. We would like to point out several significant differences between the two studies and further define the nature of inquiry.

Contrary to what the authors claimed, the Discrete Cerebral Hypothermia System used in their study is not the system used in our study. The cooling helmet and conditioning unit used by us were designed specifically for our research purposes, requiring FDA exemption. Our experimental system is not commercially available.

There are many significant differences in the two systems. For example, our conditioning unit has a constant air pressure of 26 mm Hg, more than 73% higher than the 15 mm Hg air pressure in the commercially available CoolSystem conditioning unit used in the authors’ study. The fact that the head was unshaven, combined with the much lower counter-pressure, would significantly reduce the heat transfer efficiency of the system. Due to the lower counter-pressure, the hair would maintain an air barrier between the cooling panel in the cap and the head-neck skin surface.

Further, the CoolSystem unit uses water circulated through a bath of ice cubes. This has several disadvantages. For example, the water flow seeks the path of least resistance and will therefore find open channels, most commonly occurring at the bottom of the bath where the temperature will be 3.8°C. Our cooling system used an antiseptic mix of propylene glycol and water, circulated through heat exchangers immersed vertically in the ice bath, resulting in a more evenly distributed pattern of heat exchange. The resultant temperature of the cooling cap used by the authors would therefore be higher than temperatures maintained by our system.

In addition, our conditioning system used approximately twice the volume of ice and water. This increases the ratio of ice to water, maintaining a constant bath temperature for a much longer period of use.

Such significant differences between the conditioning units alone would result in significant performance difference in achieving selective cerebral hypothermia.

The sequence of questions proposed at each stage of the investigation requires further discussion and clarifications. The strategic planning of a scientific evaluation of an externally applied selective cerebral hypothermia system should occur categorically in the following sequence:

Stage I: Proof of Concept

Questions Proposed: 1) Is it possible to have significant selective cerebral hypothermia using a head-neck surface cooling system in a realistic clinical setting yet with all conditions optimized, such as in patients with heads shaved and monitored in the intensive care unit? 2) Does it result in any local cold injuries to the skin and does it impede the standard care of such patients in the intensive care unit? 3) Does it result in delayed systemic hypothermia, thereby creating a safe therapeutic window for ultra-early delivery of head-neck regional hypothermia by emergency medical services personnel in the field?

The above questions were answered conclusively in our published study using a head-neck cooling helmet and conditioning unit that was specifically designed for the research purpose.

Stage II: Field Testing for Ultra-Early Delivery of Regional Hypothermia

Questions Proposed: 1) Could we further design a head-neck cooling system that would have enhanced heat extraction capacity to achieve sufficient intracranial cooling in field patients with heads unshaved? 2) Could we further design a head-neck cooling system to secure the cervical spine without compromising the heat extraction capacity? 3) Would the application of this newly designed system impede standard field medical evaluation and introduce other complicating factors?

We have recently secured funding to investigate the above questions.

Stage III: Outcome Study for Ultra-Early Delivery of Regional Hypothermia—A Multicenter Randomized Study

Many steps would have to occur within each stage to allow for further progress. Each study is designed to address the primary questions suitable for that stage only. Attempts to prematurely answer questions more suitable for advanced stages may introduce confusion and misinformation.

We would like to congratulate the authors on their work. As we proceed to the field testing phase of our investigation with a newly designed head-neck cooling system, we look forward to future scientific collaboration. (http://thejns.org/doi/abs/10.3171/2009.8.JNS09929)

Huan Wang, M.D.
William Olivero, M.D.
University of Illinois College of Medicine
Urbana/Champaign, Illinois
William Elkins
bioCOOL Technologies, LLC
Lincoln, California
Disclosure

William Elkins is the former chief technical officer of bio-COOL Technologies.

Reference


RESPONSE: We thank Dr. Wang and colleagues for their thoughtful comments regarding our manuscript. We would like to acknowledge our agreement with Wang et al., in that there remains a continued need for further investigation of technologies associated with selective hypothermia. The article by Wang et al., titled “Rapid and selective hypothermia achieved using a cooling helmet,” in the February 2004 edition of the Journal of Neurosurgery, introduced this technology and further informed the debate regarding the potential for benefits of cerebral hypothermia.

We would like to address the concerns of Dr. Wang and his associates regarding our recent clinical trial and article. Firstly, we agree that the system utilized in our trial is distinct from that of Dr. Wang. The manuscript does not state, nor do the authors wish to represent, that these systems are the same, only similar. The points of distinction raised are noted.

The questions posed in the letter indicate that a goal of Dr. Wang’s initial project was to determine whether it was “possible to have significant selective cerebral hypothermia using a head-neck surface cooling system in a realistic clinical setting yet with all conditions optimized…..” We too felt this was an important objective in assessing a potential device. In evaluating both effectiveness and applicability, we made the decision to not shave the patients’ heads, as this best represented the true clinical setting. Our article details our associated results and our observations regarding the relevance and implications this posed.

The other issues raised by Wang and associates in their letter are not applicable to our manuscript. Specifically, our trial did not focus on field assessment of ultra-early delivery of hypothermia. The goal of our trial was to “determine the effectiveness of the Discrete Cerebral Hypothermia System” in patients with traumatic brain injury (TBI), with primary outcomes described as “the effectiveness of the cooling cap in reducing the patient’s internal brain temperature and establishing a gradient between patients’ core and brain temperatures following TBI.” The secondary objective was an outcome analysis of “mortality, GOS, and FIM scores following severe TBI.”

We would like to thank Dr. Wang and his associates for their initial work related to regional cerebral cooling, and we wish them success in their planned investigations.

ODETTE A. HARRIS, M.D., M.P.H.
MONIQUE C. SURLES, B.S.
CARRIE R. MUH, M.D.
Emory University
Atlanta, Georgia

Reference


Hand innervation

To The Editor: I was interested to read the recently published article by Loukas et al. (Loukas M, Abel N, Tubbs RS, et al: Neural interconnections between the nerves of the upper limb and surgical implications. A review. J Neurosurg 114:225–235, January 2011), and I have a few comments.

The authors have classified communications between the median and ulnar nerve in the palm into 3 main groups incorrectly by referring to Ferrari and Gilbert. According to their classification, the first is a deep motor branch connection called the Riche-Cannieu anastomosis, the second is a deep sensory connection called the ramus communicans, and the third is a superficial sensory communication called the Berrettini branch, connecting the ulnar nerve to the third common digital palmar nerve (which arises from the median nerve). However, Ferrari and Gilbert reported 2 small communicating branches that connect the median and ulnar nerve branches in the palm: the first a deep, motor branch (the Riche-Cannieu anastomosis) and the second a superficial and sensory branch, going from the ulnar nerve to the median third common digital nerve.

The deep sensory connection between the ulnar and median nerves that has been defined as “ramus communicans” by Loukas et al. is indeed the same anatomical structure as the superficial palmar communication or the Berrettini branch. Also, the superficial communicating branch between the common digital nerves that arises from the ulnar and median nerves in the palm is called the “ramus communicans cum nervo ulnari” in Terminologia Anatomica and in anatomy atlases.

In addition, the authors have given an erroneous description when explaining the neural communications in the dorsum of the hand. Loukas et al. stated that the dorsal cutaneous branch of the ulnar nerve (DCBUN) was described by Kaplan as a branch arising from the bifurcation of the main ulnar nerve—the ramus crosses the head of the ulna dorsally and travels to the ulnar aspect of the pisiform to join the main proximal sensory branch of the ulnar nerve. The information that was given by the authors does not correspond to Kaplan’s definition. Kaplan originally described an anomalous branch of the DCBUN that crossed the ulnar head from the dorsal to the volar side, coursing to the ulnar aspect of the pisiform to join the proximal volar sensory branch of the ulnar nerve. As for the DCBUN, it leaves the main ulnar nerve at about the junction of the medial and distal thirds of the forearm. It passes distally and dorsally, deep to the flexor carpi ulnaris, perforates the deep fascia, descends along the medial side of the back of the wrist and hand, and then divides into 2, or often 3, dorsal digital nerves. It supplies sensation to the dorsoulnar aspect of the hand, dorsum of the little finger, and dorsoulnar aspect of the ring finger.

Hand innervation


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Neurosurgical forum

M. CEM BOZKURT, M.D.
Kırkkale University Medical School
Kırkkale, Turkey

Disclosure

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RESPONSE: We are in receipt of a reader’s comments regard-
ning our recently published review of neural intercom-
unications in the upper limb.3 This author, who has been 
interested in several of our recent publications, states that 
we incorrectly identified 3 subsets of ulnar-median nerve 
terconnections in the palmar hand and that the Berret-
tini branch is synonymous with the ramus communicans.
The Berrettini branch described in 1741 is a simple oblique 
near connection between the palmar ulnar and med-
ian nerves. Knowledge of this branch has evolved since 
its original depiction by Berrettini 270 years ago, and the 
many more complicated variations (horizontal, reverse, 
and so forth) of it are now more appropriately known as the 
ramus communicans.12 Similarly, although connecting the 
same nerves in the forearm, the reverse connection of the 
Martin-Gruber anastomosis is deemed the Marinacci anas-
tomosis. Additionally, this author did not like the fact that 
we referenced Kaplan3 with our description of the dorsal 
cutaneous branch of the ulnar nerve. We are quite aware 
that the Kaplan reference focuses on a variation of the in-
nervation of the dorsal ulnar skin, but within this reference 
is a very elegant description of the normal anatomy of the 
dorsal ulnar cutaneous nerve.

R. SHANE TUBBS, Ph.D.
Children’s Hospital
Birmingham, Alabama

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Chiari and duraplasty

To THE EDITOR: I read with interest the article by Bahu-
leyan et al. (Bahuleyan B, Menon G, Hariharan E V, et al: 
Symptomatic posterior fossa and supratentorial subdural 
hygromas as a rare complication following foramen mag-
um decompression for Chiari malformation Type I. Re-
The recognition of complications after surgical decom-
pression with duraplasty for Chiari malformation Type 
I (CM-I) appears to be ever increasing. Despite what 
many in the public arena and members of the medical profession 
view as a straightforward and relatively simple procedure, 
the literature continues to expand with documentation of 
complications, which, as the authors’ paper detailed, can 
be life threatening.

The authors and others2,4,5 have postulated that the 
pathogenesis of such subdural hygromas is from small 
arachnoid tears, which then create a ball-valve mechanism 
to force CSF into the subdural space, with subsequent ac-
cumulation first in the posterior fossa and then tracking 
into the supratentorial compartment.

I have treated 2 patients with CM-I who demonstrated 
subdural effusions after decompression and duraplasty and 
a generous opening of the arachnoid. A progressive supra-
tentorial hygroma developed in 1 teenager over a 5-week 
time interval (Fig. 1). Bur hole drainage and subsequent place-
ment of a subdural drain was required to ultimately resolve 
the symptoms and the effusion.

The other child, 6 years of age, demonstrated effu-
sions, which were small but accompanied by effacement 
of the basal cisterns and papilledema with symptoms of 
increased intracranial pressure (Fig. 2). This patient was 
successfully treated medically with the resolution of symp-
toms within a week of readmission to the hospital 2 weeks 
after Chiari surgery.

Both Chiari decompression procedures included a 
wide opening of the arachnoid without manipulation of 
the tonsils. Both children had pseudomeningoceles, which
were not under tension when the symptoms of increased intracranial pressure developed.

Neither of these patients had discernable hygroma in the posterior fossa, which suggests that the supratentorial effusions were not a continuation of the subdural fluid being forced rostrally by the pulsation of CSF from a tiny arachnoid tear, as suggested by the authors. There must be another mechanism at play in these situations.

One possibility is that the pseudomeningocele is acting as a sump drain drawing CSF and the cerebrum caudally and creating a larger supratentorial subdural space. Stretching and subsequent tears of small veins creating chronic hematoma/effusion is an equally logical mechanism of causation.

Whatever the mechanism at play, it is clear that duroplasty in CM-I surgery adds a serious level of potential adverse outcomes. The recent literature reflects skepticism as to the necessity of this aspect of the surgery. (http://thejns.org/doi/abs/10.3171/2011.10.JNS112288)

CLARENCE S. GREENE JR., M.D.
Children’s Hospital, New Orleans
New Orleans, Louisiana

Disclosure

The author reports no conflict of interest.

References


RESPONSE: We thank Dr. Green for sharing his experience with 2 cases of subdural hygroma (SDH) following
foramen magnum decompression (FMD). The cases presented are different from other reported cases, including ours, in that the arachnoid was widely opened during surgery and that the SDH was seen only in the supratentorial compartment.1-3

We agree with Dr. Green that our hypothesis of a ball-valve effect due to the arachnoid puncture wound cannot be applied to his cases, as the arachnoid was opened widely. We reviewed our cases and found that both had tense postoperative pseudomeningocele after FMD. The hypothesis proposed by Dr. Green—that of “the pseudomeningocele acting as a sump drain drawing CSF and the cerebrum caudally”—seems applicable for patients without posterior fossa SDHs. The sump effect creates high pressures within the posterior fossa that can displace the posterior fossa SDH. However, this mechanism fails to explain the occurrence of a posterior fossa subdural collection as was seen in our case.

The general policy for FMD at our institute for years was to perform a durotomy, open the arachnoid widely, and perform a lax duroplasty. Pseudomeningocele has been a common postoperative observation in our series, which is often asymptomatic and resolves without intervention. Therefore, we have reservations in accepting pseudomeningocele as a pivot in the development of these SDHs. Tense pseudomeningocele can be a reflection of raised intracranial pressure, but they can also be seen even in the absence of symptomatic elevated intracranial pressure.

At this point, given the paucity of cases in the literature, we believe that it is difficult to determine the exact pathophysiology behind the development of this complication. We further believe that more cases must be reported in the literature for us to know these lesions better. Because of its varied presentation, we believe that the pathophysiology behind these lesions cannot be generalized and should be considered on a case-by-case basis.

Giris Menon, M.B.B.S., M.Ch.
Biju Bahuleyan, M.B.B.S., M.Ch.
Suresh Nair, M.Ch.
Sree Chitra Tirunal Institute for Medical Sciences and Technology Trivandrum, India

References

Glioblastoma resection

To The Editor: We read with great interest the recent article by Sanai et al.1 (Sanai N, Polley MY, McDermott MW, et al: An extent of resection threshold for newly diagnosed glioblastomas. Clinical article. J Neurosurg 115:3–8, July 2011) in which the authors elaborate on the resection threshold for newly diagnosed glioblastoma multiforme (GBM). The value of extent of resection (EOR) in improving survival in patients with GBM remains controversial. In the aforementioned article, Sanai et al. offer a critical review on the methodology of earlier retrospective studies attempting to correlate EOR with survival. They performed a retrospective study of 500 newly diagnosed GBMs to relate EOR with survival. Extent of resection was determined using “3D volumetric measurement” via manual segmentation by a neurosurgeon on the basis of contrast-enhancing tissue seen on T1-weighted MR imaging and was used for further statistical analysis. They found, besides the already known independent predictors of overall survival, such as age and Karnofsky Performance Scale score, that EOR and postoperative tumor volume are independent predictors of overall survival as well. They come to the conclusion that subtotal resections ≥ 78% do significantly correspond to a survival benefit.

Although the data provided are quite convincing, the study, in our opinion, suffers from one serious limitation that the authors do not mention in their Discussion, that is, the reliability of volumetry to measure EOR of GBM. We performed a pilot study on this topic and calculated the intraclass correlation coefficient (ICC) for preoperative tumor volume (PreTV), postoperative tumor volume (PostTV), and residual tumor volume (RTV). Intraobserver agreement is high for PreTV (ICC = 0.99), PostTV (ICC = 0.73–0.94), and RTV (ICC = 0.89–0.94). Interobserver agreement is high for PreTV (ICC = 0.97) but low for PostTV (ICC = 0.54) and RTV (ICC = 0.52).

Validated response assessment criteria exist for radiotherapy and chemotherapy in patients with GBM. Unfortunately, no validated criteria are available for neurosurgical volumetric response assessment yet. Therefore, all attempts to quantify a minimally required EOR to improve survival in GBM are currently highly debatable. We need a clear definition of what to consider as (surgical) residual GBM volume and a valid method of measuring this volume if we want to discuss the added value of EOR to increase survival. A suggestion for improvement is, for example, adding more MR sequences, such as T2 and FLAIR, in the definition of RTV. Another option could be the development of an automated algorithm to define tumor volume. More research is needed to reach a valid and reliable method of defining RTV in GBM. (http://thejns.org/doi/abs/10.3171/2011.8.JNS11637a)

Pieter Kubben, M.D.
Henk van Santbrink, M.D., Ph.D.
Maastricht University Medical Center Maastricht, The Netherlands

Disclosure

Dr. Kubben is involved in a Ph.D. project on intraoperative
MRI, which is partially sponsored by Medtronic Navigation with an unrestricted grant.

References


To The Editor: First we applaud Dr. Sanai and colleagues7 efforts to identify a resection threshold in glioblastomas (Sanai N, Polley MY, McDermott MW, et al: An extent of resection threshold for newly diagnosed glioblastomas. Clinical article. J Neurosurg 115:3–8, July 2011). The topic is important, as clinical practice in terms of surgical strategies and the degree of nihilism associated with glioblastoma surgery is variable. Because of the limited available evidence, the frequency of offering only diagnostic biopsies currently varies much among centers and surgeons, as does willingness to invest time and money in aids or techniques that may increase EORs, such as fluorescence guidance or various forms of intraoperative imaging. At many centers, postoperative images are not even routinely performed, and repeat surgery is seldom the consequence if such postoperative images reveal unexpected but resectable remnants.

Sanai and colleagues’ single-center retrospective study7 included 500 patients treated between June 1997 and January 2009. They claim that an EOR as low as 78% has a statistically significant—although not necessarily clinically relevant—impact on survival. This is a much lower cutoff than reported by others,1,2 and many neurosurgeons are probably relieved that their practice of gross debulking may have an effect after all. However, can we accept these new findings?

We accept that Level I evidence on this topic will not be provided, but a retrospective study design over such a long timespan implies a great risk of detecting only reverse causation: greater EORs may generally be performed in patients with better prognoses to begin with, and both surgical treatment and adjuvant therapy have presumably improved during the study period.

A Homeogenous Study Population? To decrease the importance of potential confounders and covariates, we agree with the authors that a “large, homogeneous population of patients with GBM” would be desirable to explore a resection threshold. They claim to present a “uniform population of 500 consecutive newly diagnosed adult patients with GBM.” As pointed out in the editorial in the same issue of the Journal of Neurosurgery,6 the wide ranges in age (21–90 years), functional levels (Karnofsky Performance Scale [KPS] Scores 20–100), and tumor volumes (0.3–476.1 cm3) reveal that the study population was far from uniform. In fact, it seems almost completely unselected. As an example, the largest tumor would equal a sphere with a 9.7-cm diameter, while the smallest would only be 0.8 cm in diameter. The EORs performed are therefore far from random.

Chemotherapy and Radiation Therapy for Everyone? The authors further claim that “all patients underwent image-guided microsurgical resection followed by chemotherapy and radiation therapy.” The lower survival range was only 0.4 months—no surprise considering the diversity in functional levels and tumor sizes included. It is, however, remarkable that a patient who lived for only 12 days found time to undergo a standard regimen with radiation therapy and chemotherapy; in most clinics, that takes almost 6 weeks to complete and often is not initiated before 2–6 weeks after surgery. Further, one may wonder how the almost moribund patients with a KPS score of 20 responded to this aggressive treatment.

Standard Chemotherapy and Radiation Therapy. The authors claim that all patients received “standard chemotherapy and radiation therapy.” However, during the study period (1997–2009), standards changed a lot. Most important, temozolomide was introduced in most clinics in 2005 following the famous Stupp et al.10 study. Strong evidence supporting the use of radiotherapy in older patients was provided by a randomized controlled trial in 2007,2 but many still recommend less intense protocols in such patients. It is nevertheless known that so-called hypofractionated radiotherapy is associated with both inferior progression-free survival and overall survival.1 In other publications by Sanai et al.,7 it is evident that newer salvage treatments, such as bevacizumab, are in use at their center, increasing the diversity of treatment standards during the study period. Sanai et al. claim that “the use of different chemotherapeutic agents and radiation therapy protocols was coded for subgroup analysis, although no specific variation was predictive of outcome.” Results from such univariable analyses are unfortunately not revealed to the reader. It still seems unlikely that modern regimens are not better than old ones in a study of this magnitude, since clear benefits have been reported in multiple studies. The multivariable analysis should at the very least have included the year of treatment as a variable, as this clearly is a potential confounder.

No Developments in Surgical Therapy Since 1997? The authors report that “image-guided microsurgical resection” was performed in all patients. The use of so-called image guidance is not further explained, but there has certainly been much development in the field of image-guided neurosurgery since 1997. Again, the year of treatment should clearly have been included in their regression models. They also report that 69% of tumors were in an eloquent location (not explaining how this was classified) and that “intraoperative motor mapping was conducted in 116 patients (23%), language mapping in 43 patients (9%), and subcortical mapping in 34 patients (7%).” Thus, no mapping was used in many if not most of their eloquent tumor operations. Neither were complications, acquired deficits, and postoperative KPS scores reported in their study, al-
though the patient’s functional level is often a key factor when deciding on the intensity of adjuvant treatment and aggressiveness in surgical strategies and indications for later reoperations. Shorter survival in patients with surgically acquired deficits has also been reported.2,3 These factors have not been adjusted for in their analyses.

No Change in Treatment Attitude Since 1997? In a smaller but prospective series, we found that the aim of surgery by far was the strongest predictor of EOR,4 followed by multifocality of lesions and eloquent localization in patients with glioblastoma. Because of the developments in surgical techniques and tools along with improvements in adjuvant therapy and care, the pessimistic attitude toward therapeutic intervention in patients with glioblastoma has decreased over the years. This immeasurable change in attitude is another factor that makes it problematic to perform retrospective studies with such long time frames. At our center, this change may be exemplified in a significant rise in reoperations in later years. Reoperations were also not accounted for in the Sanai et al.7 study.

Concerning the Statistics Presented. The statistical methods used are somewhat difficult to penetrate, as the results and methods from several analyses are not presented and the explanation of the methods is quite brief. Based on our interpretation of the study methods we have the following concerns: 1) Baseline values are only provided for the whole population. The authors claim that “comparison of patient and treatment characteristics among groups was done using the Wilcoxon rank-sum test for continuous or ordinal variables,” but group sizes and tumor and patient characteristics are mandatory for meaningful interpretation of the univariable analyses provided. The authors argue that the Lacroix et al.4 study in “233 patients with newly diagnosed GBM was probably insufficiently powered, given that nearly half (46%) of the patients had a ≥ 98% tumor resection.” In the Sanai et al.7 study, however, with a 96% median EOR (range 10%–100%), how many patients had an EOR below the 78% alleged cutoff? 2) To our surprise, the 78% cutoff seems to be found in the univariable analyses only, apparently through an explorative approach with serial dichotomizations in Kaplan-Meier curves. This method does not account for confounding or effect modification by other covariates. Thus, if we understand the methods correctly, the authors seemingly did not adjust for the known major prognostic factors when searching for the cutoff value. Achieved resection grades clearly depend on several patient and tumor characteristics, making this the most important flaw in their paper. 3) In search of the resection threshold, the authors state that “serial Kaplan-Meier survival curves were generated at 2% EOR intervals.” Multiple pairwise comparisons are known to produce cumulative Type I errors with an increased risk of false-positive findings. The utilized significance test, group sizes, and confidence intervals were also not reported for their serial Kaplan-Meier survival curves. 4) When describing their recursive partitioning analysis (RPA), the authors claim that “the results exactly matched the multivariate Cox proportional hazards analysis, identifying patient age, KPS score, EOR, and tumor volume as each predictive of overall survival.” However, it seems that preoperative tumor volume was significant in the RPA, while postoperative volumes were significant in the Cox multivariate model. 5) In their introduction, the authors make good arguments against dichotomizations of continuous variables, but except for the initial Cox proportional hazards analysis, the variables are dichotomized.

All of the aforementioned factors potentially weaken the reported independent importance of EOR in the present study. Although we would like to be wrong, we believe that the alleged 78% cutoff is too optimistic. The authors claim this study to be the most rigorous effort to date to identify a resection threshold. Although reviewing over 500 patients in retrospect may be demanding, the most rigorous study to date is without a doubt based on a reanalysis of patients from the 5-aminolevulinic acid (ALA) randomized trial.9 This prospective study in a much more homogeneous population clearly provides a higher level of evidence (Level 2b vs Level 4 in the retrospective study by Sanai et al., Oxford Centre for Evidence-Based Medicine). All patients in the 5-ALA study were eligible for complete resection, and all were functionally independent prior to surgery. All patients received modern radiochemotherapy, and there was a blinded review of EOR by neuroradiologists. Analyze were stratified by age and eloquence of location. Subtotal EORs were unfortunately not associated with a survival advantage. (http://thejns.org/doi/abs/10.3171/2011.8.JNS11637b)

Disclosure
The authors report no conflict of interest.

References
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To The Editor: We read with great interest the article by Sanai et al. (Sanai N, Polley MY, McDermott MW, et al: An extent of resection threshold for newly diagnosed glioblastomas. Clinical article. J Neurosurg 115:3–8, July 2011) in which the investigators from the University of California, San Francisco (UCSF) retrospectively reviewed 500 consecutive patients with newly diagnosed GBM to determine the percentage of the contrast-enhancing part of a GBM that must be resected for a survival advantage. Using Kaplan-Meier methods, they demonstrated that “a significant survival advantage was seen with as little as 78% EOR.” In a related recursive partitioning analysis they found that “an EOR ≥ 95% had the largest impact on overall survival, with the 316 patients in this EOR category demonstrating a median survival of 14.5 months.”

The authors state that they undertook their analysis to dispel the current “all-or-none approach” that they claim has evolved from the analysis of 416 patients with GBM that was published by our group at The University of Texas MD Anderson Cancer Center over 10 years ago in the Journal of Neurosurgery. They state, “In the modern era, this report [by Lacroix et al.] serves as a critical study of reference for the neurosurgical community, justifying an ‘all-or-none’ approach commonly practiced in the surgical management of GBM.”

While we are flattered that the authors recognized the significance of our work on EOR in GBM surgery, we would like to point out that they have misrepresented both the substance and our interpretation of the data we presented in our report. Contrary to the claims of Sanai et al., no mention of an all-or-none approach to GBM management can be found in our paper. In fact, the analysis presented in Table 5 of our paper showed that as the cut-point between patients with extensive resections and those with less extensive resections was increased, the median survival for patients with extensive resections also progressively increased. This incremental increase in median survival was associated with a decreasing trend in the p value (for the test comparing survival for the 2 groups), with a significant value of p = 0.04 developing at 89% resection and progressing to p = 0.0001 at 96% and to p < 0.0001 at 97%. Although the associations between EOR and survival were not significant at all resection levels, the analysis showed a clear trend. Identification of this trend was particularly remarkable given that a 98% resection was achieved in almost half of the patients and that the median EOR in the remaining patients (that is, the < 98% group) was 88%, allowing the data set with limited power at the lower resection levels to achieve significance. The identical phenomenon was seen in a subset analysis of 233 patients with newly diagnosed GBM (Table 5), except that the p value became significant (p = 0.04) at 97% resection because of the smaller data set. These data clearly indicated that the greater the EOR the longer the survival of the patients and that every 1% of extra resection translated into an incremental increase in survival. Consistent with these data, we concluded that “the [EOR] in patients with GBM began to be associated with a survival advantage at 89% of the tumor volume.” In our subsequent analyses, the strongest effect of resection on survival was seen at a 98% resection; therefore, we used this value in our clinical outcome scale (Tables 7 and 8 in our paper).

Nevertheless, we think that the data presented by Sanai et al. are clearly of value because they reproduce our results in an independent data set and, importantly, in a population of patients with newly diagnosed GBM. In the context of our work, Sanai et al. add credence to the general concept that the greater the EOR, the better the patient survival. Indeed, they indicate that > 95% resection had the greatest effect on survival, a result that is essentially the same as our 98% resection. Likewise, their lower value of 78% resection, the point at which a statistically meaningful increase in survival was first detected, is similar to our val-
ue of 89% resection. Both of these differences are probably merely statistical phenomena resulting from differences in the data sets. Indeed, in our study, few patients had < 85% resection, whereas Sanai et al. had patients with as little as 10% resection. In the final analysis, the results reported by these authors exactly recapitulate ours and thus should not be viewed as changing the surgical management of GBMs.

While we agree with Sanai et al. that an all-or-none approach is problematic, we also think that emphasizing the 78% cutoff proposed in their paper is equally troublesome. Of greatest concern is that this value actually lowers the bar for surgical excellence and may lead practicing neurosurgeons to take the view that a 78% resection is sufficient or as good as a 98% resection. While we recognize that this is not the intent of Sanai et al., it is a possible consequence of their emphasis on a 78% resection cutoff. This interpretation must be discouraged. In the end, the message supported by the data and the one that should be emphasized to practicing neurosurgeons is that every attempt should be made to resect all of the contrast-enhancing portion of a GBM, as this approach will lead to the maximal survival. In addition, given that the contrast-enhancing portion of a tumor is composed of “tumor cells without intervening brain tissue,” the goal of complete resection is achievable in the majority of patients with GBM even when the lesion is located within or near eloquent brain. However, as we emphasized in our paper, “the optimal extent of resection in any patient depends on the tumor size and location, the patient’s general and neurological status, and the experience of the surgeon.” Therefore, if complete resection is impossible, then less complete resections as dictated primarily by functional mapping “may still provide diagnostic and symptomatic benefits.” Neurosurgeons should aim for as maximal a resection as possible without hurting the patient. Indeed, this conclusion, presented by us over 10 years ago, still holds true today.

(randomized controlled trial) in a single study with a small sample size (n = 8 patients) and should be externally validated. Although current methods could be improved, volumetric analysis of glioblastoma remains a more accurate technique than conventional 2- or 3-dimensional calculations.

Identification of an EOR Threshold. Consistent with the Lacroix et al. study, our RPA indicated that an EOR beyond 95% was associated with the greatest survival benefit. To explore the value of a subtotal resection, we performed a post hoc analysis based on the Kaplan-Meier method and found that an EOR as low as 78% may be associated with a survival benefit. Since this analysis was exploratory, it did not adjust for other putative prognostic factors due to sample size constraints. We, therefore, cannot rule out that the survival differences observed at this threshold may be driven by variables other than EOR.

Statistical Limitations Inherent to Retrospective Analysis. Our retrospective study was undertaken to define the value of EOR for patients with glioblastoma—a question that does not lend itself to a randomized trial. The statistical limitations of retrospective analysis are well known and cannot be completely controlled for with any statistical model. Nevertheless, we attempted to homogenize our data set by excluding patients with recurrent glioblastoma and maximizing the sample size. Without randomization, however, equal distribution of known and unknown confounders cannot be assured.

Taken together, our efforts to investigate the value of subtotal resection for patients with newly diagnosed glioblastoma were intended to facilitate the surgical decision-making process. Any implication that our group advocates subtotal resection of gliomas is misguided.2–3 As with any retrospective review, future studies are needed to validate the clinical relevance of our observations.
Disclosure

Dr. McDermott receives royalties from the University of California for an invention not related to this topic.

References


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Cushing disease

To The Editor: We read with interest the recently published article by Mehta et al.1 (Mehta GU, Lonser RR, Oldfield EH: The history of pituitary surgery for Cushing disease. Historical vignette. J Neurosurg 116:261–268, February 2012). The authors mentioned that the current treatment of choice for pituitary adenoma is selective adenomectomy by transsphenoidal pituitary surgery. Because their article is a historical vignette, we would like to add some important data regarding the history of transsphenoidal approach in pituitary surgery.

Almost 5000 years ago, Egyptian embalmers were the first to apply the transsphenoidal approach for brain removal without disfiguring the face during the mummification process.1,3 The Edwin Smith Papyrus is regarded as one of the most significant medical and anatomical references discovered in ancient Egypt and is considered the oldest known surgical text in the world.6 Moreover, the oldest recorded neurosurgical operation was reported in ancient Egypt circa 3000 BC.2

In 1925, Breasted met with Harvey Cushing and shared with him the first appearance of the word “brain” in ancient medical literature in the Edwin Smith Papyrus. Therefore, it is not surprising that ancient Egyptians were the first to access the brain via the sphenoid bone. It was not until the 20th century that this technique was resurrected and used to remove pituitary tumors.4

Mehta et al.5 in their historical vignette showed photographs of great neurosurgeons, such as Alfred Pattison, Howard Naffziger, Jules Hardy, Edward R. Laws Jr., and Charles B. Wilson. In the interests of historical balance or fairness, a photo or portrait of the ancient Egyptian embalmer should be placed beside these neurosurgeons as the first teacher or performer of the transsphenoidal approach for accessing the brain in history. (http://thejns.org/doi/abs/10.3171/2012.1.JNS1224)

Disclosure

The authors report no conflict of interest.

References


Response: We thank Dr. Eid and his colleagues for their interest in our report and for their summary of the early history of pituitary surgery. Of course, our focus was on the history of the management of Cushing’s disease, rather than pituitary surgery in general.

Guatemala U. Mehta, M.D.1,2
Russell R. Lonser, M.D.2
Edward H. Oldfield, M.D.1
1University of Virginia Health System
Charlottesville, Virginia
2National Institute of Neurological Disorders and Stroke
Bethesda, Maryland

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