Letters to the Editor

NEUROSURGICAL FORUM

Radiosurgery for recurrent Grade 2 meningioma

TO THE EDITOR: We read with interest the recent article by Aboukais and colleagues (Aboukais R, Zairi F, Lejeune JP, et al: Grade 2 meningioma and radiosurgery. *J Neurosurg* 122:1157–1162, May 2015).¹ In this article, the authors report on 27 patients with recurrent Grade 2 meningioma treated with radiosurgery alone. Patients were treated with a mean of 15.2 Gy. The actuarial local control rates were 75%, 52%, and 40% at 12, 24, and 36 months, respectively.

The results of this study do not significantly differ from those of other series (recently reviewed in Rogers et al., 2015²), with the exception that increased treatment doses appear to yield somewhat higher control rates than those seen in this study, as noted by the authors. The authors conclude that radiosurgery is safe and effective for local control of recurrent atypical meningiomas. While we do not dispute the lessened short-term morbidity of radiosurgery compared with surgery, particularly at the doses used in this study, we would suggest that a 40% local control rate (i.e., a 60% failure rate) at 3 years does not indicate ef-

ficacy, as suggested by the authors. For reference, we have overlaid the authors' progression-free survival Kaplan-Meier plot on the recurrence-free survival plot of Grade 2 meningiomas, which shows the course of these tumors with no treatment (Fig. 1). We acknowledge that there are limitations in this comparison, but to us, it calls into question the effect of radiosurgery on the tumor in that it does not seem to alter the natural history of the disease.

Based on this study and others, we would argue that radiosurgery alone is not sufficient therapy for Grade 2 meningiomas and should be reserved for the treatment of recurrence in patients who cannot undergo a second resection.

Phillip A. Bonney, BS

Michael E. Sughrue, MD

University of Oklahoma Health Sciences Center, Oklahoma City, OK

DISCLOSURES

The authors report no conflict of interest.

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2. Rogers L, Barani I, Chamberlain M, Kaley TJ, McDermott M, Raizer J, et al: Meningiomas: knowledge base, treatment outcomes, and uncertainties. A RANO review. *J Neurosurg* 122:4–23, 2015

Response

We would like to thank Mr. Bonney and Dr. Sughrue for taking the time to provide their insightful comments regarding our recent publication. Indeed, it is well known that surgery is the main treatment at initial management. As Grade 2 meningiomas represent severe disease and are characterized by a high rate of local recurrence, currently many authors recommend early postoperative radiotherapy to improve local control. Although the treatment of local recurrence remains controversial, we also strongly believe that surgery must be considered first when feasible. Nevertheless, poor general condition and tumor location near to critical structures are likely to dramatically increase surgical morbidity, making some patients not suitable for such strategy. As described in our article, the vast majority of patients included in our series harbored tumor recurrences located in a critical zone, such

FIG. 1. Kaplan-Meier plot demonstrating recurrence-free survival (solid line) of patients with Grade 2 meningiomas (modified with permission from Fig. 34.4, from Perry A, Meningiomas, in McLendon RE, Rosenblum MK, Bigner DD (eds): *Russell & Rubenstein's Pathology of Tumors of the Nervous System*, ed 7. London: Hodder Arnold, 2006, pp 427–468) with overlaid local progression-free survival (dashed line) presented by Aboukais et al., 2015.¹ The similarity of these plots may suggest that the natural growth of these tumors is altered little by radiosurgery.

Meckel's cave, the sagittal sinus, or the cavernous sinus. Only 4 patients had recurrences located on the convexity; 3 of these patients had previously undergone multiple surgical procedures and radiation therapy, and 1 patient was 79 years old and had limited autonomy. The treatment of tumor recurrence in such situations is challenging and requires consideration of other therapeutic options, such as radiosurgery. In our study, we aimed to evaluate the efficiency of radiosurgery in patients not suitable for surgery who had clear evidence of tumor recurrence. Indeed, the 12-, 24-, and 36-month actuarial local control rates were 75%, 52%, and 40%, and we stated that radiosurgery was a "safe and effective treatment for local control of delayed progression after resection of a Grade 2 meningioma." These results are modest but involve patients for whom therapeutic options were very limited. Our conclusion was based on our results, and also on the literature review, which reported improved local tumor control likely due to increased treatment doses. In the study by Choi and colleagues,¹ the 12-, 24-, and 36-month actuarial local control rates were 100%, 100%, and 73%, with a mean dose of 22 Gy. Therefore, the major lesson of our study was to increase the prescribed dose to almost 20 Gy.

Like the authors, we believe that "radiosurgery alone is not sufficient therapy for Grade 2 meningiomas" and we place major hopes on the emergent medical therapies.²

Rabih Aboukais, MD

Fahed Zairi, MD

Jean-Paul Lejeune, MD, PhD

Emilie Le Rhun, MD

Maximilien Vermandel, PhD

Serge Blond, MD, PhD

Patrick Devos, PhD

Nicolas Reyns, MD, PhD

Lille University Hospital, Hôpital Nord, Lille, France

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Innovations in neurosurgery

TO THE EDITOR: We would like to comment on the article by Marcus et al.¹ (Marcus HJ, Hughes-Hallett A, Kwasnicki RM, et al: Technological innovation in neurosurgery: a quantitative study. *J Neurosurg* 123:174–181, July 2015) that was recently published in the *Journal of Neurosurgery*. In this study the authors searched a pat-

ent database to identify the top-performing patent codes, which were subsequently grouped into "technology clusters." Concurrently, they queried PubMed to identify peer-reviewed publications. Patents and publications were used as metrics of technological development and clinical translation. The top-performing technology clusters identified using this methodology were image-guidance devices, clinical neurophysiology devices, neuromodulation devices, operating microscopes, and endoscopes. This article represents one of the first attempts to quantitatively evaluate technological innovation in the field of neurosurgery.

There are several aspects of this article's methodology that we feel should be critiqued. First, the authors declare they searched for "granted patents," but the description in the *Methods* section is insufficient to confirm that the search strategy included the patent codes for granted patents. Furthermore, the authors later describe compiling the "codes . . . for which the greatest number of patent applications had been submitted," implying applications not granted patents. The authors compiled the "top 50 performing patent codes." This is confusing, as "code" implies the type of patent document. Patent "classifications" are the US or International class codes that specify a subject area. Patent classifications would be meaningful to this analysis; patent codes less so.

The number of filed patents is used in this analysis as a proxy for technological advancement. This number can be highly influenced by factors relating to changes in patent law—for example, the change in patent terms in 1995, or with the more recent change from "first to invent" to "first to file." These changes in patent law should be factored out. Moreover, filing patent applications costs a fair amount of money. Thus, the availability of funds can influence the number of patent applications rather than solely their "innovation impact." Medtronic may have had an outsized influence on the results set, as a large commercial enterprise with plenty of funds would inherently be expected to file many patents.

Next, medical procedures themselves are not patentable. Therefore, using patents to track innovation may create an inherent bias against other contributions to changes in clinical practice. If the authors' definition of innovation in clinical practice was limited to new technology, this definition would neglect any non-technological advancement.

The database utilized in this study is problematic as well. The database (DOCDB) does not contain the full text of patents nor the claims, only bibliographic data and abstracts. The appearance of key words in granted patent claims would be of more value than the appearance of key words in an abstract. Additionally, DOCDB is also a worldwide database. The data would be highly redundant, and the innovation sought by the authors is more likely to be centered in the US and Europe.

Lastly, the lead time from patent filing to clinical application is likely to be on the order of several years, and perhaps as long as a decade. Thus, today's clinical advances would be related to a cluster of patents filed sometime around 2005. Further examination of this phenomenon would be interesting. Marcus et al. quantitatively evaluated technological innovation in the field of neurosurgery,

but their article has several limitations as noted above. Developing the specific methodology to forecast the potential influence of technology clusters will be important as the field of neurosurgery continues to advance.

At our institution, we have developed a program called NeuroInnovations. Several of our faculty members have filed intellectual property that has been licensed by large companies or spun out into startups. The goal of the program is to help educate and teach the common hurdles entrepreneurs face when launching a new venture or technology. Intellectual property is certainly one significant challenge, but one must also consider other factors—including regulatory, reimbursement, feasibility, timeline, funding, clinical trial design, to name a few—that can sometimes thwart even the best ideas that are published in the patent literature. By better understanding the process of innovation, future generations of neurosurgeons and bioengineers can address the most compelling unmet clinical needs and together advance the standard of care.

S. Harrison Farber, BS

Steven Thomas, MS

Gary Pace, PhD, JD

Shivanand P. Lad, MD, PhD

Duke University Medical Center, Durham, NC

DISCLOSURES

The authors report no conflict of interest.

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Response

We would like to thank Farber et al. for their interest in our study, and the Editor for allowing us the opportunity to respond.

Although innovation may broadly include any intervention that alters practice, the stated focus of our work was technological innovation—the development of new devices. Patents represent a relevant, reliable, and readily available metric of technological innovation.²

The PatentInspiration database (AULIVE, Ypres, Belgium) used in the study is based on the DOCDB database, which contains bibliographic data from over 90 countries, but also contains full text (claims and descriptions) of the main searched authorities (including the World Intellectual Property Organization, European Patent Office, United States of America, and Canada). We searched the database for patents granted that related to neurosurgery, and subsequently grouped these patents into technology clusters using the patent class codes that specify relevant subject areas.

A number of factors may influence the number of patents granted, leading to an exponential rise in both patent and publication counts over time. To this end, we used a previously described equation to normalize both patent and publication counts using data from 2010 (the year reporting the greatest number of patents and publications).¹

There is invariably a lag between patent application

and granting; this is an inherent limitation of the study methodology and was acknowledged as such in the article. Nonetheless, the most important technology clusters identified over the 50-year study period are likely to remain valid, including image-guidance devices, clinical neurophysiology devices, neuromodulation devices, operating microscopes, and endoscopes.

Future advances in operative neurosurgery will probably result as much from further technological innovation as from a greater understanding of the basic pathophysiological processes underlying neurological ill health—the gaps in knowledge in the latter are a very important limitation in achieving enhanced outcomes following neurosurgical intervention. We would like to take this opportunity to congratulate Farber et al. on their NeuroInnovations program, and would encourage the development of similar programs that aim to overcome the barriers to clinical translation from bench to bedside.

Hani J. Marcus, MRCS^{1,2}

Archie Hughes-Hallett, MRCS¹

Richard M. Kwasnicki, PhD¹

Ara Darzi, FRS¹

Guang-Zhong Yang, FEng¹

Dipankar Nandi, DPhil²

¹The Hamlyn Centre, Institute of Global Health Innovation, Imperial College London, London, United Kingdom

²Imperial College Healthcare NHS Trust, London, United Kingdom

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Nonsurgical acute traumatic subdural hematoma

TO THE EDITOR: We read with great interest the article published in the *Journal of Neurosurgery* by Bajsarowicz et al.¹ (Bajsarowicz P, Prakash I, Lamoureux J, et al: Nonsurgical acute traumatic subdural hematoma: what is the risk? *J Neurosurg* **123**:1176–1183, November 2015). Their goals were to establish what proportion of patients are initially treated conservatively, to determine what proportion of patients will deteriorate and require surgical evacuation, and to identify risk factors associated with deterioration and delayed surgery in 869 patients. They reported that 74.3% (646 patients) were initially treated conservatively and only 6.5% eventually required delayed surgery. They compared multiple factors between patients who required delayed surgery and patients without sur-

gery. The authors concluded that patients with a larger subdural hematoma (SDH), a lesion located at the convexity, alcohol abuse, and repetitive falls have the highest risk for deterioration. There was no significant difference with regard to age, sex, Glasgow Coma Scale score, Injury Severity Score, abnormal coagulation, use of blood thinners, and presence of cerebral atrophy or white matter disease. We thank Bajsarowicz et al. for this valuable study; however, we believe that some points require clarification.

According to Taussky et al., the presence of comorbid diseases such as diabetes mellitus, hypertension, atrial fibrillation, and coronary artery disease had no significant effect on mortality in patients who underwent craniotomy for acute traumatic SDH.² Taussky et al. studied patients older than 65 years.

On the other hand, the effect(s) of comorbid diseases on deterioration was not mentioned in the study reported by Bajsarowicz. We think that the effects of these comorbid diseases should be studied to evaluate the presence of any effect on deterioration in such a big series. We think this is important because, as is known, hypertension especially is a recognized risk factor for both ischemic and, in particular, hemorrhagic events.⁴ Fluctuations in blood pressure may increase the existing SDH. Additionally, the neurotoxic effects of hyperglycemia are well known.³

Tugay Atalay, MD
Hakan Ak, MD

School of Medicine, Bozok University, Yozgat, Turkey

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Disclosures

The authors report no conflict of interest.

Response

We thank Drs. Atalay and Ak for their interest in our work. As mentioned in their letter, we looked at multiple factors for a potential interaction with traumatic SDH expansion and rebleeding. The presence of diabetes mellitus, hypertension, atrial fibrillation, and coronary artery disease were not specifically addressed in our series. However, their indirect effect on brain parenchyma was evaluated with the presence or absence of white matter disease. White matter disease was not found to have any impact on SDH deterioration. Another potential factor for SDH rebleeding is the fact that patients with conditions such as atrial fibrillation and coronary artery disease may normal-

ly take antiplatelet aggregation agents or anticoagulants. We did look at the intake of prophylactic anticoagulant, therapeutic anticoagulant, and antiplatelet aggregation agents in the acute phase. Therapeutic anticoagulation and antiplatelet therapy were rarely used and therefore those data did not reach any statistical significance in this large series. Prophylactic anticoagulation was used more often, but it had no effect on the rate of deterioration requiring surgical intervention.

Atalay and Ak also point out that fluctuations of systemic blood pressure could play a role in the SDH expansion. Indeed, it is known that hypertension in the perioperative period of a craniotomy is associated with acute hemorrhagic complications.¹ The effect of chronically poorly controlled hypertension on the evolution of a traumatic SDH after the acute period has never been studied to our knowledge, and it may have an effect on the membrane microvasculature's tendency to rebleed. Unfortunately, these data could not be captured in the current study because many of these patients did not have continual blood pressure monitoring. This would indeed be an interesting aspect to examine in future studies.

Judith Marcoux, MD, MSc, FRCSC

Rajeet Singh Saluja, MD, FRCSC

McGill University Health Centre, Montreal, Quebec, Canada

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Intraoperative detection of glioma cells by flow cytometry

TO THE EDITOR: We read with great interest the recent article by Diaz et al.⁴ investigating the mechanism of tumor delineation by unconjugated fluorescein in the brain (Diaz RJ, Dios RR, Hattab EM, et al: Study of the biodistribution of fluorescein in glioma-infiltrated mouse brain and histopathological correlation of intraoperative findings in high-grade gliomas resected under fluorescein fluorescence guidance. *J Neurosurg* 122:1360–1369, June 2015). The authors studied the fluorescein uptake in normal human astrocytes, in U251 glioma cells, in intracranial U87 malignant glioma xenografts, and in 12 patients who underwent fluorescein-guided resection of their high-grade gliomas using low-dose intravenous fluorescein and a microscope-integrated fluorescence module. The results showed that fluorescein demarcation of glioma-invaded brain is the result of distribution of fluorescein into the extracellular space, most likely as a result of an abnormal blood-brain barrier (BBB). There was no tumor cell-specific uptake of fluorescein, and tumor cells appeared to exclude fluorescein for the most part.⁴

The extent of glioma resection is of paramount importance for a patient's prognosis. Currently, we are investigating the value of cell cycle analysis for rapid intraoperative characterization of brain tumors and for the identification of tumor margins.¹⁻³ By modifying a previously published protocol reported by our group, we are able to provide, within 6 minutes, rapid cell cycle analysis.¹ Based on G₀/G₁, S-phase, G₂/M phase fraction, and ploidy status, high-grade tumors could be differentiated from low-grade tumors and neoplastic from normal brain tissue with high sensitivity and specificity, both for adult and pediatric brain tumors.^{1,3} Shioyama et al. also demonstrated that flow cytometry may be feasible to determine the presence of glioma in a surgical biopsy sample.⁵ Furthermore, we proposed the development of a device that would combine the Cavitrion ultrasonic surgical aspirator with a real-time flow cytometer. This device would permit complete resection of the tumor and could be a breakthrough in intraoperative guidance for brain tumor removal.⁶

First, compared to fluorescein-guided resection, which is limited to areas with BBB disruption because there is no fluorescein uptake in tumor cells, cell cycle analysis by flow cytometry has the ability to readily identify cancer cell populations based on their abnormal cell cycle and DNA ploidy. Second, given that low-grade tumors might not produce BBB disruption and thus fluorescein uptake, flow cytometry can be applied to low-grade tumors because these tumors have an abnormal cell cycle, and in some cases exhibit hypoploidy. Third, flow cytometry does not require the administration of any pharmaceutical compound to the patient and it is widely available. Finally, the addition of a multiparameter flow cytometry immunophenotyping technique could provide analysis of specific tumor cell markers that would further improve the accuracy in recognizing tumor cells. In conclusion, cell cycle analysis by flow cytometry might be useful for the intraoperative assessment of tumor margins, thus facilitating complete tumor excision. This might be a novel field for flow cytometry and deserves to be further investigated.

George A. Alexiou, MD, PhD

George Vartholomatos, PhD

Spyridon Voulgaris, MD, PhD

Athanassios P. Kyritsis, MD, PhD

University Hospital of Ioannina, Ioannina, Greece

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Disclosures

The authors report no conflict of interest.

Response

I sincerely appreciate the thoughtful letter sent by Dr. Alexiou and his colleagues. Their team has done pioneering work in cell cycle analysis, using flow cytometry for evaluation of tumor margins in surgery.

I agree with the authors that fluorescein fluorescence is only the beginning of our quest for intraoperative delineation of the brain-tumor borders. More specifically, fluorescein fluorescence is used because more accurate technology such as that discussed by Dr. Alexiou and his colleagues is not actively pursued in the US. I look forward to a further description of flow cytometry for intraoperative tumor work. My team is also in the process of using mass spectrometry in the operating room for refining the detection of tumor margins.

Aaron Cohen-Gadol, MD, MSc

Goodman Campbell Brain and Spine, Indianapolis, IN

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