Neurosurgical Forum

LETTERS TO THE EDITOR

Error in obituary

TO THE EDITOR: I read with deep interest the obituary on Charles B. Wilson submitted by Dr. Berger, Ms. Garner, and Dr. McDermott¹ (Berger MS, Garner IV, McDermott MW: Obituary. Charles B. Wilson, MD, 1929–2018. *J Neurosurg* 129:547–550, August 2018). Dr. Wilson was a legend in his own time, and though many of his residents have achieved extraordinary success, his influence extended far beyond his immediate program and trainees.

I wish to correct a minor error on the second page, second paragraph: “In 1958, Wilson became the first neurosurgical resident at the VA Medical Center of New Orleans, working under Lewellyn Rayburn and maintaining his interest in both pathology and gliomas.” The correct name for the attending neurosurgeon is Raeburn C. Llewellyn, MD. Dr. Llewellyn was chief of the Tulane University Division of Neurosurgery during my years in Tulane Medical School from 1970 to 1973. He was pivotal in my decision to include an application for neurosurgery residency at the University of Kentucky, where he said two of his former residents, Charles B. Wilson and Horace A. Norrell, relocated from New Orleans, receiving appointments to the neurosurgery faculty. Dr. Llewellyn was born in Corbin, Kentucky, attended medical school at the University of Virginia, and did his neurosurgery training in New Orleans. He was on the Tulane faculty from 1960 to 1979. Dr. Llewellyn passed away in New Orleans in 2009 at 89 years of age.²

James R. Bean, MD

Neurosurgical Associates, Baptist Health Medical Group, Lexington, KY

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Disclosures

The author reports no conflict of interest.

Correspondence

James R. Bean: james.bean@bhsi.com.

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Response

We thank Dr. Bean for the correction regarding the correct name of Dr. Llewellyn. We would also like to thank Dr. John J. Moossy, who submitted a letter to the *Journal of Neurosurgery* editorial office stating that his father's name was also misspelled in the obituary.

The record is now correct.

Mitchel S. Berger, MD

Ilona V. Garner, BS

Michael W. McDermott, MD

University of California, San Francisco, CA

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Cafeteria approach to management of trigeminal neuralgia: stereotactic radiosurgery as a preferred option

TO THE EDITOR: We have read with great interest the article by Tuleasca and colleagues³ (Tuleasca C, Régis J, Sahgal A, et al: Stereotactic radiosurgery for trigeminal neuralgia: a systematic review. *J Neurosurg* [epub ahead of print April 27, 2018. DOI: 10.3171/2017.9.JNS17545]).

Trigeminal neuralgia (TN) has always been a disease of conflict from pathological and treatment perspectives. Despite advances in radiological imaging, evidence from autopsy studies, and intraoperative findings, concrete answers are still not in sight. A cafeteria approach ranging from conservative treatment (medications) through minimally invasive surgery (radiosurgery, radiofrequency ablation, etc.) to microvascular decompression (MVD) in itself shows that we are still missing something. Gamma Knife surgery (GKS) has been considered a natural extension to microneurosurgery, and its role in the management of typical TN has been both competitive and supplemental to microsurgical interventions. Neurosurgeons in the currently practicing generation are mostly familiar with all of the management options, and most have an inherent bias in deciding on management plans as per availability of treatment options (such as radiosurgery),

cost-effectiveness analysis, personal experience, and acceptance of the risk-benefit ratio in an Internet-savvy patient population. TN remains one of the most common neurosurgical ailments attracting medicolegal lawsuits against the practitioners.² The comparable success rate of radiosurgery without the surgical risks has made GKS a preferred treatment modality among the majority of the patient population.³

This systematic literature review by Tuleasca et al. has provided evidence-based recommendations, which definitely enrich the existing literature and help in guiding treatment options in different clinical settings. The authors advise not irradiating a longer length of the trigeminal nerve to minimize the Flickinger effect (level I evidence) and using a single 4-mm collimator shot without any beam blocking. A longer length increases the chance of sensory dysfunction in the form of hypesthesia in the trigeminal nerve distribution, which we have also observed personally. However, hypesthesia is rarely bothersome to the patients, as the pain relief is better with longer length exposed. Still, MVD is considered to be the reference treatment modality (especially in the younger population), although the surgical approach is relatively technically demanding and involves risk. On the other hand, GKS is a safe, repeatable, and cost-effective technique. Whether MVD should always be preferred in the younger age group remains a debatable question, as GKS provides similar pain relief to this population and patients can safely undergo MVD in the event of radiosurgical failure. It has already been proven that post-GKS MVD does not entail any additional technical difficulty beyond MVD as initial treatment and its safety has been demonstrated. Another highlighted point is superiority of GKS over linear accelerator (LINAC) and CyberKnife radiosurgery with less complication of bothersome hypesthesia (level III evidence). An anterior point with higher radiation dose (90 Gy) should be preferred (level II and III evidence).^{1,3}

The authors should be congratulated for their extensive review of the published literature on this common disease. Similar reviews should be solicited on secondary trigeminal neuralgias and atypical trigeminal neuralgias for better understanding and evidence-based management.

**Manjul Tripathi, MCh
Aman Batish, MS**

Postgraduate Institute of Medical Education and Research,
Chandigarh, India

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Disclosures

The author reports no conflict of interest.

Correspondence

Manjul Tripathi: drmanjultripathi@gmail.com.

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Response

We thank Drs. Tripathi and Batish for their interest and support with regard to our recently published paper in the *Journal of Neurosurgery*. Drs. Tripathi and Batish mention several technical nuances of radiosurgery in TN. One is to irradiate a longer length of the treated nerve. However, the Flickinger trial¹ (prospective, double-blind, and randomized) clearly advocated for an identical pain relief for 1 versus 2 isocenters radiosurgery, while complications may be increased using 2 isocenters. Another issue is that GKS would be a safe, repeatable, and cost-effective treatment. The safety and efficacy of GKS is now well demonstrated, even on a long-term basis.^{4,8} Nevertheless, repeat GKS is associated with a higher rate of sensory dysfunction and should be performed cautiously and only if a first GKS has been effective for a long period.⁹ Performing an MVD after prior GKS has been considered more surgically challenging by some authors.³

The eternal debate of the reference technique (especially MVD or radiosurgery) will persist in the absence of a randomized trial, which is difficult to organize due to multiple issues. The only prospective, non-randomized trial comparing MVD and GKS was published by Linskey et al.⁵ After a mean follow-up period of 3.4 ± 2.14 years, the initial and last follow-up pain-freedom rates were 100% and 80.6% for MVD and 77.3% and 45.5% for GKS, respectively. Pollock et al.⁷ addressed the same issue in patients less than 70 years old undergoing posterior fossa exploration or GKS. After a mean follow-up of 25.5 months, the patients who had undergone MVD more commonly had pain relief without medication. We do agree that MVD involves several risks, which have already been underscored. It is still considered the reference technique by several authors, as it addresses what one would consider as the underlying cause of this disease (e.g., the neurovascular conflict).

Each of the techniques available for treatment of TN has its own application, depending on the characteristics of the individual patient (i.e., intensity of pain, response to and tolerance of medication, medical comorbidities, expectations, involvement of different branches of the trigeminal nerve—factors defining the algorithm of treatment). When the neurosurgical unit treating the patient has access to all techniques, the most appropriate one can be chosen.²

We thank Drs. Tripathi and Batish for their appreciation of our work. We continue to strive to provide our patients with evidence-based care in the framework of a personalized approach.⁶ The “cafeteria approach,” as the authors nicely called it, should be adapted to the patient’s particular case, while accurately explaining the safety and efficacy of each approach. In this spirit, the surgical management of TN should be evidence-based, with radiosurgery being one of the interventional alternatives. The authors of these guidelines have remained impartial, as their role was not to favor one technique over another, but to present objective data and correct scientific interpretation.

Constantin Tuleasca, MD^{1-3,9}Jean Régis, MD¹⁰Arjun Sahgal, MD⁴Antonio De Salles, MD⁵Motohiro Hayashi, MD⁶Lijun Ma, PhD^{7,8}Roberto Martínez-Álvarez, MD⁹Ian Paddick, MSc¹³Samuel Ryu, MD¹¹Ben J. Slotman, MD, PhD¹²Marc Levivier, MD, PhD⁹¹Centre Hospitalier Universitaire Vaudois, Neurosurgery Service and Gamma Knife Center, Lausanne, Switzerland²Medical Image Analysis Laboratory (MIAL), Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland³Signal Processing Laboratory (LTS 5), Ecole Polytechnique Fédérale de Lausanne (EPFL), Lausanne, Switzerland⁴University of Toronto, Sunnybrook Odette Cancer Centre, Toronto, ON, Canada⁵University of California Los Angeles, CA⁶Tokyo Women's Medical University, Tokyo, Japan⁷Kyoto University, Kyoto, Japan⁸University of California San Francisco, CA⁹Ruber International Hospital, Madrid, Spain¹⁰Timone University Hospital, Aix-Marseille University, Marseille, France¹¹Stony Brook University, Stony Brook, NY¹²VU University Medical Center, Amsterdam, The Netherlands¹³National Hospital for Neurology and Neurosurgery, London, United Kingdom

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Preoperative seizures as predictive sign of brain invasion by meningioma

TO THE EDITOR: I read with interest the article by Hess et al.⁸ reporting association of perioperative seizures and brain invasion by meningioma (Hess K, Spille DC, Adeli A, et al: Brain invasion and the risk of seizures in patients with meningioma. *J Neurosurg* [pub ahead of print April 27, 2018. DOI: 10.3171/2017.11.JNS172265]). In their study, the frequency of symptomatic epilepsy before surgery was 32% and 18% in patients with, respectively, invasive and non-invasive tumors ($p = 0.033$), and detection of brain invasion was more frequent if preoperative seizures were noted (OR 2.57; $p = 0.025$). The authors have claimed, “for the first time (to our knowledge), we investigated correlations of brain invasion with tumor and edema volumes and the risk of perioperative seizures in a large series of patients with meningioma.” Hopefully, they will not be too disappointed to know that very similar results have been already reported by our group and published elsewhere.³⁻⁵

We evaluated the role of single-voxel proton magnetic resonance spectroscopy in preoperative assessment of 100 intracranial meningiomas and peritumoral brain,^{5,7} and research protocol presumed prospective collection of multiple clinical, radiological, surgical, and histopathological factors. Among various results, our study revealed a statistically significant association between the presence of preoperative seizures and invasive growth of the neoplasm, a predictive sign (to the best of our knowledge) not reported previously. Its positive and negative predictive values were, respectively, 0.82 and 0.58 in the entire series (100 cases)⁵ and 0.89 and 0.58 if the cohort was limited to newly diagnosed convexity and parasagittal meningiomas (49 cases).^{3,4} However, similar interrelationships were found for several other investigated factors (Table 1), and after their combined evaluation in a multivariate model only peritumoral edema preserved its statistically significant association with brain invasion by the neoplasm.⁵ In corroboration of our results, Hess et al.⁸ have noted statistically significant independent associations of symptomatic epilepsy with rising tumor volume ($p = 0.042$) and brain invasion ($p = 0.009$), but it remains unclear how this variable (“preoperative seizures”) behaved in multivariate analysis of factors associated with brain invasion itself.

Two aforementioned studies differ in evaluation of the tumor/edema size and brain invasion. We assessed largest diameter of meningioma and used modified Kazner classification for grading peritumoral edema.^{6,7,9} In contrast, Hess et al.⁸ measured 3 perpendicular diameters of the tumor and calculated corresponding volumes according to

TABLE 1. Evaluation of diagnostic factors for identification of meningiomas with macroscopically invasive growth

Diagnostic Factor	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Odds Ratio	p Value*	p Value**
Male sex	0.35 (0.21–0.49)	0.86 (0.76–0.96)	0.68 (0.49–0.87)	0.60 (0.49–0.71)	3.21 (1.16–8.88)	0.0385 ^a	0.3181
Symptomatic epilepsy	0.21 (0.09–0.30)	0.96 (0.91–1.00)	0.82 (0.59–1.00)	0.58 (0.47–0.69)	6.22 (1.26–30.64)	0.0308 ^a	0.1746
Largest diameter of the tumor						0.0105 ^b	
7 cm and more	0.12 (0.02–0.22)	0.96 (0.91–1.00)	0.71 (0.37–1.00)	0.55 (0.44–0.66)	3.09 (0.57–16.84)		
6 cm and more	0.23 (0.10–0.36)	0.90 (0.82–0.98)	0.67 (0.43–0.91)	0.57 (0.46–0.68)	2.67 (0.83–8.55)		
5 cm and more	0.37 (0.23–0.51)	0.73 (0.61–0.85)	0.55 (0.37–0.73)	0.57 (0.45–0.69)	1.64 (0.68–3.98)		
4 cm and more	0.74 (0.61–0.87)	0.53 (0.39–0.67)	0.58 (0.45–0.71)	0.70 (0.55–0.85)	3.29 (1.36–7.97)		0.2984***
3 cm and more	0.95 (0.88–1.00)	0.18 (0.07–0.29)	0.51 (0.40–0.62)	0.82 (0.59–1.00)	4.61 (0.94–22.68)		
Irregular shape of the tumor	0.42 (0.27–0.57)	0.82 (0.71–0.93)	0.67 (0.49–0.85)	0.62 (0.50–0.74)	3.20 (1.25–8.22)	0.0251 ^a	0.1009
Moderate-to-severe peritumoral edema	0.42 (0.27–0.57)	0.94 (0.87–1.00)	0.86 (0.71–1.00)	0.65 (0.54–0.76)	11.04 (2.96–41.15)	0.0001 ^a	0.0021

Reprinted from *Clin Neurol Neurosurg* 113(3), Chernov et al., 1H-MRS of intracranial meningiomas: What it can add to known clinical and MRI predictors of the histopathological and biological characteristics of the tumor? 202–212, Copyright 2011, with permission from Elsevier.

Borders of the 95% confidence interval are marked in parentheses.

* In univariate analysis (according to ^achi-square test with continuity correction and ^bMann-Whitney test).

** In multiple logistic regression analysis.

*** This cut-off level was chosen because it provides the greatest sum of sensitivity and specificity in univariate analysis.

the formula for ellipsoid. Such a technique is sufficiently precise in cases of round or oval lesions but may be less suitable for irregular ones. Also, we relied on macroscopic intraoperative assessment of brain invasion (although detailed histopathological investigation was done in all cases), whereas Hess and associates based their determination of invasion on microscopic findings.^{1,8} Since both methods have some pitfalls, their combined use is preferable.²

Overall, I wish to congratulate our colleagues on their excellent investigation, and I feel rather encouraged by independent confirmation of our original finding that the presence of symptomatic epilepsy may be associated with invasive growth of meningioma. Detailed characterization of this possible predictive sign certainly requires prospective analyses. Nevertheless, it may have important clinical implications, since currently brain invasion is considered as sufficient criterion for diagnosis of atypical meningioma (WHO grade II).¹⁰ Additional studies should clarify whether the presence of seizures negatively impacts progression-free survival of patients with meningioma undergoing observation or radiosurgery.

Mikhail F. Chernov, MD, DMedSci

Tokyo Women's Medical University, Tokyo, Japan

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Disclosures

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Correspondence

Mikhail F. Chernov: m_chernov@yahoo.com.

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Response

I would like to cordially express my appreciation of this well-elaborated letter from Dr. Chernov and his efforts to provide additional and critical analysis of our results.

Indeed, we found a distinctly higher risk of preoperative seizures in patients with brain invasive meningiomas as compared to individuals with non-invasive meningiomas. Accordingly, we stated that consideration of preoperative seizures during communication between the neurosurgeon and the neuropathologist might increase the sensitivity of the detection of brain invasion in microscopic analyses, which—in contrast to macroscopic invasion—directly impacts grading and potentially adjuvant treatment.³ Moreover, intraoperative evaluation of brain invasion by the neurosurgeon based on the “cleavability” of the tumor remains controversial¹ and—in contrast to brain invasion in microscopically analyzed specimens—is not clearly defined.⁴ Hence, we exclusively focused on microscopically detected brain invasion. However, being aware of the work of Chernov et al., we pointed out that our finding was in accordance with results from their analyses based on the macroscopic evaluation of brain invasion and explicitly mentioned Dr. Chernov’s letter in the *Discussion*.² Hence, although we appreciate his concerns, there is no disappointment of us to be worried about.

With great interest we saw the results from the Tokyo group reporting several MRI characteristics found to be associated with macroscopically brain invasive growth as summarized in the current letter. We recently identified (aside from other variables) an increasing peritumoral edema volume and an irregular tumor shape but not a larger tumor volume as predictors for microscopically detected brain invasion in a series of over 600 intracranial meningiomas. However, in multivariable analyses, only an increasing edema volume was confirmed to predict brain invasion independent of other grading criteria. The corresponding manuscript has been submitted and is currently under revision, so explicit data cannot be given here. Moreover, we and others revealed male sex as an additional risk factor for microscopically brain invasive growth.^{5–7} The similarity of these results with the findings from Chernov et al. is remarkable, suggesting that the intraoperative macroscopic assessment of microscopic brain invasion might be more precise than actually supposed. Hence, we agree that consideration of intraoperative and radiological findings might increase the sensitivity of the detection in microscopical analyses. While these hypotheses remain to be clarified in future analyses, we are glad to know that the issue of the clinical relevance of brain invasion in meningiomas is emphasized by other groups.

Benjamin Brokinkel, MD

University Hospital Münster, Münster, North Rhine-Westphalia, Germany

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Laser ablation after stereotactic radiosurgery

TO THE EDITOR: I read with great interest the article by Ahluwalia et al.¹ (Ahluwalia M, Barnett GH, Deng D, et al: Laser ablation after stereotactic radiosurgery: a multicenter prospective study in patients with metastatic brain tumors and radiation necrosis. *J Neurosurg* [epub ahead of print May 4, 2018; DOI: 10.3171/2017.11.JNS171273]). Having treated post-stereotactic radiosurgery (SRS) brain metastases in multiple ways, including via laser interstitial thermal therapy (LITT), I am intrigued by the emerging data on the role of LITT in this patient population.^{2–5} I disagree with the authors’ conclusion that “LITT is a low-risk surgical procedure” that “should be considered in those who are surgically eligible.” The study does not present sufficient evidence to support the broad use of LITT over craniotomy for post-SRS brain metastases and demonstrates less efficacy than would be expected for treatment with craniotomy.

Thirty-seven percent of patients were lost to follow-up at 12 weeks and 62% of patients were lost to follow-up at 26 weeks. Given this amount of discontinuation in a study that started with 44 patients, it is challenging to draw any conclusions. That said, the patient population is relatively healthy for a cohort of individuals with brain metastases with a mean age of 58.5 years and exclusion criteria that included serious systemic medical illnesses and the need for ongoing anticoagulation or antiplatelet therapy. Within this group of favorable surgical candidates, 12% experienced an immediate neurological complication and 33% had surgery-related adverse effects. These complication rates are higher than what would be expected for similar patients undergoing craniotomy.^{7–9}

A key differentiator between LITT and craniotomy is the degree of postoperative cerebral edema, and the subsequent requirement of corticosteroids, and this topic was not addressed in the article. Following intracranial laser ablation the lesion initially increases in size, and subse-

quent lesion size reduction occurs over the following 3–60 days.⁶ There is an inflammatory reaction in the perilesional normal brain and resultant cerebral edema that persists until the lesion abates. This results in a corticosteroid requirement often up to or longer than 1 month. This contrasts with a craniotomy for lesion resection that may cause increased cerebral edema from surgical manipulation for 24 hours and typically results in a rapid reduction in cerebral edema and the need for corticosteroids over 1 week. Of note, only 31% of patients were able to stop or reduce steroid usage at the 12-week follow-up, again a stark contrast to what would be expected following a craniotomy for lesion resection.

A clinical trial directly comparing LITT to craniotomy for post-SRS brain metastases would be incredibly useful. Although LITT has proven to be an exciting new neurosurgical tool, the current evidence, including this article, does not support its broad use when treating post-SRS brain metastases, and its role in this patient population may be limited to smaller, deep-seated lesions. The degree of cerebral edema created by LITT versus the reduction in cerebral edema following craniotomy is a key advantage of craniotomy for this pathology.

Andrew J. Fabiano, MD

Roswell Park Comprehensive Cancer Center, Buffalo, NY
SUNY at Buffalo Jacobs School of Medicine, Buffalo, NY

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Disclosures

The author reports no conflict of interest.

Correspondence

Andrew J. Fabiano: andrew.fabiano@roswellpark.org.

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Response

Thank you to Dr. Fabiano for his letter about the Laser Ablation After Stereotactic Radiosurgery (LAASR) study.

While we agree that the rate of loss to follow-up was high in this study, similar findings have been noted in other trials in patients with brain metastases, which is a concern especially because neurocognition and quality of life is important in this patient population. In the landmark trial on the effect of SRS alone versus SRS with whole-brain radiation therapy (WBRT) on cognitive function in patients with 1–3 brain metastases, the primary endpoint was cognitive deterioration at 3 months.² Only 79 of the 111 patients randomized to SRS alone and 72 of the 102 randomized to SRS plus WBRT completed the 3-month evaluation, indicating an approximately 30% drop-off at 12 weeks. The patients in the SRS versus SRS plus WBRT study were an upfront brain metastases population, and the patient population in the LAASR study are those in whom prior SRS failed; hence they were a sicker patient population by definition.

Similarly, the proposed comparison to the surgical literature provided is not appropriate because LITT is being used for metastases in which radiosurgery has failed and not as first-line treatment of patients with single intracranial lesions. What was noted in this study is important: sick patients, especially those with multiple brain metastases, have a hard time following up in the study scenario. There are no data in the literature to show rates of accrual and drop-out for craniotomy as studied in our trial. In addition, rates of surgery-related complications are also not comparable to the literature cited because the patient population studied in the LAASR trial is a group with dismal outcomes and who are intrinsically at high risk for complications even without surgery. The only comparative study available in the literature is a meta-analysis of LITT versus craniotomy for high-grade glioma by Barnett et al., and the rate of major complications for LITT was less than half the rate for craniotomy (5.7% vs 13.8%).¹

What this effort emphasized is that patients who otherwise might not entertain surgery are willing to consider a minimally invasive surgical procedure. For the majority of these patients, especially those with radiation necrosis, an excellent outcome can be achieved. Evidence from the epilepsy literature shows clearly how much easier recovery from LITT is than recovery from a craniotomy.³ The patient populations that are agreeing to undergo LITT are therefore not likely to be the same as those agreeing to craniotomy. Although a randomized study is theoretically ideal to compare the two tools, in our experience there is a high likelihood that accrual to this study would be difficult given the perceived differences in the invasiveness of the procedures by the patient.

Manmeet S. Ahluwalia, MD
Cleveland Clinic, Cleveland, OH

Veronica L. Chiang, MD
Yale University, New Haven, CT

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Gamma Knife surgery for trigeminal pain due to benign and malignant skull base tumors

TO THE EDITOR: We have read with great interest the recent article by Phan et al.,⁵ discussing the role of Gamma Knife surgery (GKS) for trigeminal neuralgia (TN) secondary to recurrent malignant skull base tumors (Phan J, Pollard C III, Brown PD, et al: Stereotactic radiosurgery for trigeminal pain secondary to recurrent malignant skull base tumors. *J Neurosurg* [epub ahead of print April 27, 2018. DOI: 10.3171/2017.11.JNS172084]). The authors nicely discuss tumor control, symptom palliation, and opioid use/dependency.

The authors' study highlights several important aspects. First, it underlines the role of single-fraction GKS as a primary treatment option for recurrent malignant skull base tumors in the context of secondary TN. Furthermore, in selected cases, the Extend system (Elekta AB) was used for hypofractionation. The potential role of the new Gamma Knife model ICON (Elekta) should also be underscored for this indication, because it allows frameless stereotactic treatment using a combination of cone-beam CT (CBCT), a thermoplastic mask system (allowing replacement in well-selected cases of the Leksell stereotactic G frame), and an infrared-based high-definition motion management camera system for patient tracking during treatment delivery.⁸ In fact, the ICON nicely combines the flexibility of the mask and CBCT with the well-known remarkable dose distribution and steep dose fall-off of the GKS treatment.⁸ Second, there is a need for tumor targeting and oncological control as a primary outcome. In cases of TNs related to benign skull base tumors, a wide variety of technical nuances have been reported, including initial targeting of the tumor only,⁷ targeting of the tumor and the nerve dur-

ing the same session,² and targeting of tumor and nerve at different time points.^{4,7} This makes the analysis of the outcomes, in terms of safety and efficacy, more difficult. Third, there is a radiobiological rationale that explains a more rapid decrease in lesion size compared with that of benign tumors, which would also explain, in some instances, the quick relief with regard to the nerve compression and further symptom alleviation. It is now well established that malignant tumors have higher α/β ratios, estimated to be closer to 10 and representative of early-responding tissues, whereas slow-growing benign brain tumors such as pituitary adenomas, arteriovenous malformations, and benign meningiomas have lower α/β ratios, estimated to be closer to 3 and representative of late-responding tissues.^{1,3,6}

In conclusion, the report by Phan et al.⁵ underlines the potential role of GKS in new indications, including skull base malignancies in patients with trigeminal pain, as in the context of a combined management for residual tumors after surgery and/or in cases of recurrence (Fig. 1). It also highlights the fact that GKS remains "an optimal skull base" tool due to its steep gradient, allowing optimal tumor coverage while sparing and/or improving neurological function. Furthermore, in benign, tumor-related secondary TN, the current literature is heterogeneous and does not answer to three essential questions: when (at what exact time point), what (is it the tumor? is it the nerve? both?), and how to target (retrogasserian versus root entry zone, etc.). On the other hand, in malignant skull base tumors, local control is the primary aim, and so there is limited room for technical nuances.

Constantin Tuleasca, MD¹⁻³

David Patin⁴

Marc Levivier, MD, PhD, IFAANS^{1,2}

¹Lausanne University Hospital (CHUV), Department of Clinical Neurosciences, Neurosurgery Service and Gamma Knife Center, Lausanne, Switzerland

²University of Lausanne (Unil), Faculty of Biology and Medicine (FBM), Lausanne, Switzerland

³Ecole Polytechnique Fédérale de Lausanne (EPFL), Signal Processing Laboratory (LTS5), Lausanne, Switzerland

⁴Institute of Radiation Physics, Lausanne, Switzerland

Acknowledgments

Lausanne University Hospital.

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FIG. 1. Targeting of a metastasis of the Meckel's cave from a pulmonary carcinoma (**upper left**), of a meningioma of the petrous apex (**upper center**), of a trigeminal schwannoma (**upper right**), and of an arteriovenous malformation (**lower left and right**) (all cases were symptomatic with a TN, which further resolved after GKS treatment). Figure is available in color online only.

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Correspondence

Constantin Tuleasca: constantin.tuleasca@gmail.com.

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Response

We thank Dr. Tuleasca and coauthors for their kind comments and interest in our study. This manuscript was written shortly after FDA clearance of the Gamma Knife ICON model (Elekta AB), and therefore the patients included in this study were largely treated with frame-based, single-fraction Gamma Knife radiosurgery (GKS), with 4 cases treated with fractionated GKS using the Extend immobilization system. As the authors from Lausanne have nicely summarized, the Gamma Knife ICON has a mask-based immobilization system, an infrared-based high-definition motion management system to track intrafraction

motion, and cone beam CT image guidance. This system has the potential to deliver frameless single- and multi-fraction GKS and can be considered for use in the treatment of malignant skull base tumors causing trigeminal pain, as described in this article. We agree the patients in this study treated with Gamma Knife Extend (end-to-end accuracy < 2 mm)^{1,3,5} are also appropriate candidates for treatment with the ICON system. A potential advantage of the ICON system is increased tolerability and comfort with a frameless mask system. In our experience, the Extend system requires candidates to have calm demeanors, good dentition due to a vacuum-assisted bite block with custom prosthesis, and to be absolute non-gaggers.

As Tuleasca et al. appropriately alluded to, our goal and intent for each case is to treat the entire tumor to establish oncological control. There were a few exceptions when the entire tumor was not treated because the area in question was near a critical structure and not conclusively identified as tumor on imaging. However, in retrospect, these areas likely harbored tumor and subsequently progressed on MRI. This supports a major theme in this study that it is necessary to completely cover the tumor, and a frank discussion with the patient should take place regarding the potential toxicity risks associated with reirradiation. We believe one of the significant findings in this study is that among those with radiographic evidence of tumor control after GKS, there is a significant palliative impact that is clinically measurable in terms of improved pain control and reduction in opioid requirement. We hypothesize that the facial pain is associated with the rapid growth observed with most malignant tumors and agree with our colleagues from Lausanne that the higher α/β ratios of these malignant tumors likely explain the pain relief and reduction

in opioid analgesics that can be observed by 3 months posttreatment. Conversely, worsening of facial pain after a period of stability or improvement can be a harbinger of tumor progression.

A particular challenge with skull base reirradiation is the delivery of tumoricidal dose without exceeding the cumulative dose tolerance of nearby critical structures. This is further complicated by the likelihood that recurrent malignant tumors after prior conventionally fractionated (approximately 2 Gy per fraction) radiotherapy will harbor radioresistant clonogens. Thus, it is generally accepted that ablative doses with a high biologically effective dose (BED) are needed to achieve good tumor control. However, the optimal BED for malignant skull base tumors is yet to be determined. In our study, the median prescription dose of 17 Gy prescribed to the 50% isodose line in single-session-GKS patients corresponded to a mean dose > 27 Gy and calculated BED₁₀ > 90 Gy. A similar BED is calculated for fractionated GKS when using 24 Gy in 3 fractions prescribed to the 46% isodose line. Extrapolating from the non-small cell lung cancer stereotactic body radiation therapy (SBRT) data, a BED > 100 Gy is required to achieve > 90% local control.⁶ Similarly, SBRT studies for recurrent squamous cell carcinomas of the head and neck suggest a BED > 90 Gy is associated with improved local control.^{2,4}

Lastly, we believe the mean dose and BED received by the entire target volume (margin tumor dose) should also be considered when evaluating a GKS plan. Even when the prescribed dose is the same, the mean and maximum doses received by the tumor volume can be very different, depending on factors such as dose distribution, shot placement, and choice of prescription isodose line. Evaluating the optimal BED as well as the BED and mean dose to the tumor in those patients with in-field recurrences are the subject of our current research.

Courtney Pollard III, MD, PhD
Jing Li, MD, PhD
Caroline Chung, MD, MSc, FCRP
Franco DeMonte, MD
Jack Phan, MD, PhD

University of Texas MD Anderson Cancer Center, Houston, TX

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EVD clamp trials and ventriculoperitoneal shunt insertions in patients with nontraumatic SAH

TO THE EDITOR: We are thankful to Ascanio et al.¹ for their work on nontraumatic subarachnoid hemorrhage (SAH) (Ascanio LC, Gupta R, Adeeb N, et al: Relationship between external ventricular drain clamp trials and ventriculoperitoneal shunt insertion following nontraumatic subarachnoid hemorrhage: a single-center study. *J Neurosurg* [epub ahead of print March 16, 2018. DOI: 10.3171/2017.10.JNS171644]). They conducted a retrospective review of all consecutive patients with nontraumatic SAH complicated by acute hydrocephalus who were admitted over a period of 10 years to a single major academic institution in the United States. After considering the exclusion criteria, 114 patients who underwent external ventricular drain (EVD) insertions during the first 24 hours after admission and who underwent at least 1 clamp trial prior to removal were included in the final analysis. Through this paper the authors delivered a crucial message that failure of initial EVD clamp trials in such patients “does not necessarily indicate that the patient should receive a shunt,” which is commendable. However, some points are worth mentioning with respect to the methodology and findings in this study.

First, the inclusion of patients with EVD infections in the final sample size is debatable. In the setting of an EVD infection, there would be a change in the entire line of management with respect to CSF diversion. The process of clamping will have to be discontinued because the patient cannot receive a shunt irrespective of the result of the clamp trial. Also, an increase in length of ICU stay is likely in this subset of patients. Hence, the presence of EVD infection anytime during the hospital stay could have been an exclusion criterion.

Second, there is evidence in the literature to suggest that surgical clipping of ruptured intracranial aneurysms may be associated with a lower risk of shunt-dependent hydrocephalus.^{2,3} Varelas et al.,⁶ in their retrospective study involving 188 patients, found that permanent shunting was associated with coiling. They postulated that during clipping, blood or clots may have been evacuated from the subarachnoid space, which is not possible in an endovascular approach. However, in the paper by Ascanio et al., the authors remain silent with respect to the method

used for securing ruptured aneurysms. An inhomogeneity in the patient population with regard to this characteristic may have confounded the results of the study.

Last, in patients who underwent surgical clipping, the question of whether lamina terminalis fenestration was performed is a factor that deserves a mention. Fenestration of the lamina terminalis can reduce the rates of shunt-dependent hydrocephalus, although there is still conflicting evidence in this regard.^{4,7} A prospective randomized controlled trial such as the ongoing FISH trial⁵ could help settle this debate.

Nitish Agarwal, MBBS

Amol Raheja, MCh

All India Institute of Medical Sciences, New Delhi, India

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Correspondence

Amol Raheja: dramolraheja@gmail.com.

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Response

We thank Agarwal and Raheja for their comments on our recent publication, “Relationship between external ventricular drain clamp trials and ventriculoperitoneal

shunt insertion following nontraumatic subarachnoid hemorrhage: a single-center study.”

In our original analysis, we assessed the relationship between the EVD clamp trials and ventriculoperitoneal (VP) shunt insertion following nontraumatic SAH, and showed that 38.9% of patients who underwent a third clamp trial did not require a VP shunt.

Seventeen (14.9%) patients had their aneurysm secured with microsurgical clipping; 74 (64.9%) were managed endovascularly with coils, stent-assisted coils, or the Pipeline embolization device; 21 (18.4%) were managed expectantly; and 2 (1.8%) had combined surgery and endovascular treatment. We compared the VP shunt rates between patients who underwent microsurgical clipping and those who received endovascular treatment. In the endovascular group, 32 (43.2%) patients received a VP shunt compared to 4 (23.5%) patients in the clipping group ($p = 0.13$). Similarly, Nam et al.⁶ reported a VP shunt insertion rate of 18.7% in the clipping group and 21.8% in the coiling group ($p = 0.31$). In contrast, Varelas et al.⁷ reported that coiling was independently associated with increased risk of VP shunt insertion on multivariable analysis (OR 6.35, 95% CI 1.3–29.0; $p = 0.02$). However, this study had some methodological limitations, which requires caution in interpreting the result. The results of their univariable analysis implicating coiling as a risk factor for VP shunt insertion are not reported. Furthermore, the criteria used in constructing the multivariable analysis are unknown. On the other hand, our data are concordant with theirs,¹ regarding EVD placement as a risk factor for a VP shunt insertion ($p = 0.01$), which was also found in other studies.^{3,8} In fact, our group developed^{4,5} and validated^{1,2} a predictive scoring system for VP shunt insertion following SAH, which uses EVD insertion as a key component.

One concern raised by Agarwal and Raheja is that we included 13 patients with EVD infection in the study, which may have biased the results. We compared the number of clamp trials between patients who had EVD infection and those who did not have an EVD infection ($p = 0.52$). Although this analysis may not fully answer the concerns raised, we conducted a sensitivity analysis excluding the patients with EVD infection. One hundred one patients were included. The median number of EVD clamp trials was 2 (range 1–4). Forty-one patients underwent VP shunt insertion. The proportion of patients who underwent 3 clamp trials and avoided VP shunt placement was 35.3%.

TABLE 1. Clamp trials and VP shunt in patients without EVD infection

No. of Clamp Trials	VP Shunt		Total Patients	OR (95% CI)
	Yes	No		
1	15 (32.6%)	31 (67.4%)	46	—
2	14 (40%)	21 (60%)	35	1.37 (0.55–3.44)
3	11 (64.7%)	6 (35.3%)	17	3.74 (1.17–12.21)*
4	1 (33.3%)	2 (66.7%)	3	1.03 (0.087–12.319)
Total	41 (100%)	60 (100%)	101	

Values are the number of patients, unless otherwise indicated.

* $p = 0.06$.

The odds ratio in this group of getting a VP shunt compared to those who underwent 1 clamp trial is 3.74 (95% CI 1.17–12.21; $p = 0.06$) (Table 1). These findings are similar to what we found in the original analysis of the entire group. The median number of days in the ICU was 15 for 1 clamp trial, 16 for 2 clamp trials, 15 for 3 clamp trials, and 24 for 4 clamp trials ($p = 0.48$). Again, these findings are similar to what we found in our original analysis.

With regard to lamina terminalis fenestration, this procedure is not routinely performed in our institution.

Luis C. Ascanio, MD¹

Raghav Gupta, BS¹

Nimer Adeeb, MD²

Justin M. Moore, MD, PhD^{1,3}

Christoph J. Griessenauer, MD⁴

Julie Mayeku, MD¹

Yaw Tachie-Baffour, BS¹

Ranjit Thomas¹

Abdulrahman Alturki, MBBS, FRCSC^{1,5}

Philip G. R. Schmalz, MD⁶

Christopher S. Ogilvy, MD¹

Ajith J. Thomas, MD¹

¹Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA

²Louisiana State University Health, Shreveport, LA

³Boston Medical Center, Boston University, Boston, MA

⁴Geisinger Medical Center, Danville, PA

⁵The National Neuroscience Institute, King Fahad Medical City, Riyadh, Saudi Arabia

⁶University of Alabama, Birmingham, AL

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