Neurosurgical Forum

LETTERS TO THE EDITOR

Methodological advances in randomized trials

TO THE EDITOR: We enjoyed reading the paper by Mansouri et al.¹¹ and the accompanying editorial by Barker¹ (Mansouri A, Cooper B, Shin SM, et al: Randomized controlled trials and neurosurgery: the ideal fit or should alternative methodologies be considered? *J Neurosurg* 124:558–568, February 2016). We entirely agree with their conclusion that “given the role of RCTs [randomized controlled trials] as one of the highest levels of evidence, it is critical to improve on their methodology and reporting.”¹¹ In this letter, we highlight a number of recent methodological advances that have the potential to improve the quality of neurosurgical randomized trials and clinical research in general.

Firstly, we believe that the IDEAL (Idea, Development, Exploration, Assessment, Long-term study) framework, which describes the 5 stages through which surgical innovation normally passes, is a very useful guide for surgeons interested in evaluating surgical interventions—both new and established.¹³ The international IDEAL Collaboration (<http://www.ideal-collaboration.net>) offers recommendations for all stages of surgical innovation, from the initial idea (Stage 1) to the established and accepted procedure subjected to long-term studies (Stage 4), and accepts that different study designs and methods of reporting are needed for the various stages, since each stage has unique characteristics. Importantly, it recognizes that during the development stage (Stage 2a), innovations undergo rapid iterative change in the light of accumulating experience, limiting the usefulness of randomized trials. Hence, it supports prospective development studies at this stage, with “sequential reporting of all cases and outcomes without omissions, and with clear explanations of when and how technique, design, or indications were changed.”¹⁴ Moreover, it recognizes that randomized trials should be used whenever possible to investigate effectiveness (Stage 3) but also suggests a number of solutions for overcoming common issues in surgical trials (that is, surgeon preferences, patient preferences, quality control of intervention) and a number of alternatives when a traditional randomized trial is not feasible.¹⁴

Secondly, in recent years the importance of using standardized sets of outcomes, known as “core outcome sets” (COSs), in effectiveness trials has been increasingly recognized. Heterogeneity in the outcomes measured is a

well-documented phenomenon that leads to considerable difficulties with evidence synthesis. In addition, outcome-reporting bias, which is a “results-based selection for publication of a subset of the original measured outcomes variables,” is a significant problem.¹⁶ The consensus-based development and use of a COS, which as a minimum should be measured and reported in all trials for a specific clinical area, can address these well-known problems. Recent progress in the field of COSs is exemplified by the work undertaken by the COMET (Core Outcome Measures in Effectiveness Trials) Initiative (<http://www.comet-initiative.org>), an international group that brings together people interested in the development and implementation of agreed-to COSs for clinical research. The initiative conducts methodological work on COS development and supports a COS database that allows developers to register new projects to avoid unnecessary duplication.⁶ We consider the involvement of patients and caretakers as stakeholders to be important in COS development. For example, the ongoing CODE-CSDH (Core Outcomes and Common Data Elements in Chronic Subdural Haematoma) project will involve these groups as well as health care practitioners and researchers in the development of a COS for chronic subdural hematoma.⁴

Importantly, the IDEAL framework and the use of COSs are gaining support from funding bodies. The National Institute for Health Research (NIHR) Health Technology Assessment program in the United Kingdom (UK) recently issued, based on the IDEAL framework principles, a call for proposals for prospective collaborative cohort studies of fenestrated endovascular aneurysm repair for juxtarenal abdominal aortic aneurysms. In addition, the same body has added the following statement to its application forms: “Where established Core Outcomes exist they should be included amongst the list of outcomes unless there is good reason to do otherwise.”¹⁶

Thirdly, in the UK there has also been investment in trials methodology research by the Medical Research Council and the formation of 5 hubs. For example, the ConDuCT-II (Collaboration and Innovation in Difficult and Complex Randomised Controlled Trials in Invasive Procedures) Hub for Trials Methodology Research in Bristol (<http://www.bristol.ac.uk/social-community-medicine/centres/conduct2/>) has a specific focus on creating new and better methods for the design and conduct of randomized trials in surgery.

Fourthly, a national program for surgical trials has been developed in the UK.¹² In 2012, the Royal College of Sur-

Centre for Surgical Research, School of Social and Community
Medicine, University of Bristol, United Kingdom

Peter McCulloch, FRCS
University of Oxford, United Kingdom

geons of England (RCS) along with partners established a network of surgical trial units across the UK and appointed surgical specialty leads (SSLs) from the various surgical specialties with the “specific remit to develop new trials, establish clinical networks, and work with their patients to develop and deliver innovative trials across the surgical disciplines.”^{12,15} Trainee research collaboratives, networks of trainees working together to design and deliver multicenter trials and high-quality prospective studies, are at the foundation of this national program.² In neurosurgery, the British Neurosurgical Trainee Research Collaborative (BNTRC; <http://www.bntrc.org.uk>) was formed in April 2012 with the support of the Society of British Neurological Surgeons (SBNS) and the Neurosurgical RCS SSL.¹⁰ More than 1800 patients undergoing 2 of the commonest neurosurgical procedures (evacuation of chronic subdural hematoma and ventriculostomy) have been enrolled in the 2 first prospective, UK-wide, observational cohort studies designed by the BNTRC.^{5,9} In addition, funding was secured from the NIHR Health Technology Assessment program for 2 randomized trials in collaboration with the SBNS Neurotrauma Group. The RESCUE-ASDH (Randomised Evaluation of Surgery with Craniectomy for Patients Undergoing Evacuation of Acute Subdural Haematoma) trial (craniotomy vs hemicraniectomy for acute subdural hematoma; <http://www.rescueasdh.org>) has now rolled out to 21 UK units,⁸ while the Dex-CSDH trial (Dexamethasone for Adult Patients With a Symptomatic Chronic Subdural Haematoma; 2-week tapering course of dexamethasone vs placebo for patients with chronic subdural hematoma treated in neurosurgical units) started recruitment in August 2015.⁷ All of these studies are recruiting patients to schedule and are supported in all participating units by a consultant (that is, board-certified neurosurgeon) principal investigator and at least 1 trainee (that is, resident) co-principal investigator.

Finally, we would like to endorse Dr. Barker's statement that “in 2015, no form of medical publication rivals the RCT for academic and ‘real world’ clinical impact.”¹ Pragmatic randomized trials—aiming to compare 2 or more treatments in the real world—are a form of comparative effectiveness research (CER), the so-called experimental CER.³ In our view, the latter together with nonexperimental CER (for example, registry-based observational studies) provides neurosurgeons with the necessary tools to evaluate established and novel therapeutic interventions. However, we strongly believe that surgeons should aim to work with multidisciplinary teams to design and conduct pragmatic randomized trials when a research question is sufficiently refined to allow for the design and conduct of such studies.

Angelos G. Kolias, MRCS

Peter J. Hutchinson, FRCS(SN)

Addenbrooke's Hospital & University of Cambridge, Cambridge
Biomedical Campus, United Kingdom

Dion G. Morton, FRCS

University of Birmingham, United Kingdom

Jane M. Blazeby, FRCS(Gen Surg)

References

1. Barker FG II: Editorial. Randomized clinical trials and neurosurgery. **J Neurosurg** **124**:552–557, 2016
2. Bhangu A, Kolias AG, Pinkney T, Hall NJ, Fitzgerald JE: Surgical research collaboratives in the UK. **Lancet** **382**:1091–1092, 2013
3. Chalkidou K, Tunis S, Whicher D, Fowler R, Zwarenstein M: The role for pragmatic randomized controlled trials (pRCTs) in comparative effectiveness research. **Clin Trials** **9**:436–446, 2012
4. Chari A, Hocking KC, Broughton E, Turner C, Santarius T, Hutchinson PJ, et al: Core outcomes and common data elements in chronic subdural hematoma: a systematic review of the literature focusing on reported outcomes. **J Neurotrauma** [epub ahead of print], 2015
5. Coulter IC, Kolias AG, Marcus HJ, Ahmed AI, Alli S, Al-Mahfoudh R, et al: Proposal for a prospective multi-centre audit of chronic subdural haematoma management in the United Kingdom and Ireland. **Br J Neurosurg** **28**:199–203, 2014
6. Gargon E, Williamson PR, Altman DG, Blazeby JM, Clarke M: The COMET initiative database: progress and activities update (2014). **Trials** **16**:515, 2015
7. ISRCTN Registry: A randomised, double blind, placebo-controlled trial of a two-week course of dexamethasone for adult patients with a symptomatic chronic subdural haematoma (Dex-CSDH trial). (<http://www.isrctn.com/ISRCTN80782810>) [Accessed January 20, 2016]
8. ISRCTN Registry: Randomised evaluation of surgery with craniectomy for patients undergoing evacuation of acute subdural haematoma (RESCUE-ASDH). (<http://www.isrctn.com/ISRCTN87370545>) [Accessed January 20, 2016]
9. Jamjoom AA, Kolias AG, Zaben M, Chari A, Kitchen J, Joannides A, et al: External ventricular drainage: Is it time to look at national practice? **Br J Neurosurg** [epub ahead of print]
10. Kolias AG, Jones TL, Cowie CJ, Coulter IC, Afshari FT, Tarnaris A, et al: A report from the inaugural meeting of the British Neurosurgical Trainee Research Collaborative held in the Royal College of Surgeons of England, 19 October 2012. **Br J Neurosurg** **27**:307–310, 2013
11. Mansouri A, Cooper B, Shin SM, Kondziolka D: Randomized controlled trials and neurosurgery: the ideal fit or should alternative methodologies be considered? **J Neurosurg** **124**:558–568, 2016
12. McCall B: UK implements national programme for surgical trials. **Lancet** **382**:1083–1084, 2013
13. McCulloch P, Altman DG, Campbell WB, Flum DR, Glasziou P, Marshall JC, et al: No surgical innovation without evaluation: the IDEAL recommendations. **Lancet** **374**:1105–1112, 2009
14. McCulloch P, Cook JA, Altman DG, Heneghan C, Diener MK: IDEAL framework for surgical innovation 1: the idea and development stages. **BMJ** **346**:f3012, 2013
15. Royal College of Surgeons of England: Surgical clinical trials. (<https://www.rcseng.ac.uk/surgeons/research/surgical-research/surgical-clinical-trials>) [Accessed January 20, 2016]
16. Williamson PR, Altman DG, Blazeby JM, Clarke M, Devane D, Gargon E, et al: Developing core outcome sets for clinical trials: issues to consider. **Trials** **13**:132, 2012

Disclosures

Angelos Kolias is the IDEAL Collaboration specialty lead for neurosurgery and served as the inaugural chair of the British Neurosurgical Trainee Research Collaborative from 2012 to 2015. Peter Hutchinson is supported by an NIHR Research Professorship and the NIHR Cambridge Biomedical Research Centre and is the neurosurgical specialty lead, RCS Clinical Research Initiative. Dion Morton is the director of clinical research, RCS. Jane Blazeby is a member of the COMET Initiative management group and director of the Medical Research Council ConDuCT-II Hub for Trials Methodology Research in Bristol. Peter McCulloch is the chair of the IDEAL Collaboration steering group.

Response

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

INCLUDE WHEN CITING

Published online March 11, 2016; DOI: 10.3171/2015.12.JNS152894.

©AANS, 2016

Transsphenoidal surgery for nonfunctioning adenomas

TO THE EDITOR: We read with great interest the recent article by Pledger et al.⁴ comparing postoperative sinonasal quality of life (QOL) in adult patients surveyed after undergoing microscopic sublabial transsphenoidal surgery (n = 33) or endoscopic endonasal transsphenoidal surgery (n = 46) for pituitary adenomas (Pledger CL, Elzoghby MA, Oldfield EH, et al: Prospective comparison of sinonasal outcomes after microscopic sublabial or endoscopic endonasal transsphenoidal surgery for nonfunctioning pituitary adenomas. *J Neurosurg* [epub ahead of print December 11, 2015]. DOI: 10.3171/2015.6.JNS142695). Their study addresses the important topic of patients' perceptions of their own recovery from surgery, which supplements the objective end points that surgeons tend to study. Indeed, nasal morbidity is a primary source of postoperative morbidity in such patients.

This single-center study examined 2 common transsphenoidal approaches. Each approach was performed by a single surgeon. A third commonly performed variation is the microscopic direct endonasal approach, which was not studied by Pledger et al. As surgeons who have performed all 3 approaches at some point in our careers, we have found that the sublabial approach is the most invasive of these 3 approaches because it requires a sublabial incision and extensive dissection of the nasal septal mucosa. However, it is notable that late sinonasal outcomes (i.e., at 1-year follow-up) in the study by Pledger et al. were similar for the 2 approaches, although short-term (i.e., at 24–48 hours, 2 weeks, and 8 weeks) sinonasal outcomes favored the endoscopic approach. This similarity in outcomes illustrates the robust capacity of the sinonasal cavity to heal after surgery.

We recently completed a collaborative multicenter prospective study (Rhinological Outcomes in Endonasal Pituitary Surgery [clinical trial no. NCT01504399, clinicaltrials.gov]) examining QOL in patients undergoing either the direct microscopic approach or the endonasal endoscopic approach.¹ This study enrolled more than 200 patients, included baseline and longitudinal data for 6 months, and had greater than 90% patient follow-up. The large sample size and good follow-up increased the power of the study compared to that of the current study by Pledger et al. We also examined the predictors of sinonasal QOL in the patients in our cohort who underwent endoscopic surgery.² We learned that patients who underwent an endoscopic approach had a slight QOL advantage at 3 months, but we found no difference at later (e.g., 6-month) follow-up. In addition, sinonasal QOL was a strong predictor of overall QOL and recovery. This association reinforces the notion that in the early postoperative period, sinonasal QOL is closely correlated with how patients feel about their overall recovery. We also learned, as in the study by Pledger et al., that there is an initial worsening of sinonasal symptoms after the surgical procedure, but that patients typically recover by approximately 3 months. This pattern of initial worsening and recovery is now well documented.

Through the works of Pledger et al., those of our team, and those of several other groups cited in the article by Pledger et al., the predictors of sinonasal QOL are becoming clearer. These predictors include not only the surgical visualization method, but also the age and sex of the patient, treatment of the middle turbinate, use of the expanded endonasal approach, use of absorbable nasal packing, use of a septal flap, and development of postoperative sinusitis. Increased understanding of these factors will help surgeons to better counsel their patients, and also will improve surgical techniques to optimize QOL. Last, additional QOL scales with improved validity for this specific patient population continue to be developed.³

Andrew S. Little, MD

Barrow Neurological Institute, St. Joseph's Hospital and Medical Center,
Phoenix, AZ

Daniel F. Kelly, MD

Garni Barkhoudarian, MD

Brain Tumor Center, John Wayne Cancer Institute, Santa Monica, CA

References

1. Little AS, Kelly DF, Milligan J, Griffiths C, Prevedello DM, Carrau RL, et al: Comparison of sinonasal quality of life and health status in patients undergoing microscopic and endoscopic transsphenoidal surgery for pituitary lesions: a prospective cohort study. *J Neurosurg* **123**:799–807, 2015
2. Little AS, Kelly D, Milligan J, Griffiths C, Prevedello DM, Carrau RL, et al: Predictors of sinonasal quality of life and nasal morbidity after fully endoscopic transsphenoidal surgery. *J Neurosurg* **122**:1458–1465, 2015
3. Little AS, Kelly D, Milligan J, Griffiths C, Rosseau G, Prevedello DM, et al: Prospective validation of a patient-reported nasal quality-of-life tool for endonasal skull base surgery: The Anterior Skull Base Nasal Inventory-12. *J Neurosurg* **119**:1068–1074, 2013

4. Pledger CL, Elzoghby MA, Oldfield EH, Payne SC, Jane JA Jr: Prospective comparison of sinonasal outcomes after microscopic sublabial or endoscopic endonasal transsphenoidal surgery for nonfunctioning pituitary adenomas. **J Neurosurg** [epub ahead of print December 11, 2015. DOI: 10.3171/2015.6.JNS142695]

Disclosures

The authors report no conflict of interest.

Response

We thank Drs. Little, Kelly, and Barkhoudarian for their thoughtful comments, and we agree with their statements regarding patient recovery following transsphenoidal surgery. Patients undergoing endoscopic transsphenoidal surgery for nonfunctioning pituitary adenomas appear to recover more quickly than those who undergo microscopic techniques. However, long-term sinonasal recovery was not found to differ significantly between approaches. Because the lasting sinonasal results appear similar, we continue to advocate that surgeons choose the visualization tool (microscope or endoscope) based on their experience and ability to effectively remove the tumor.

John A. Jane Jr., MD
Edward H. Oldfield, MD
Carrie L. Pledger, MA

University of Virginia Health System, Charlottesville, VA

INCLUDE WHEN CITING

Published online March 18, 2016; DOI: 10.3171/2015.12.JNS152965.

©AANS, 2016

Repair of skull base defects

TO THE EDITOR: With interest, I read the article by Safavi-Abbasi et al.¹⁷ (Safavi-Abbasi S, Komune N, Archer JB, et al: Surgical anatomy and utility of pedicled vascularized tissue flaps for multilayered repair of skull base defects. *J Neurosurg* [epub ahead of print November 27, 2015. DOI: 10.3171/2015.5.JNS15529]). The authors discussed the versatility of temporalis muscle fascia and laterally pedicled pericranial flaps in the reconstruction of the middle cranial fossa floor and essentially reviewed the literature on the subject. It is rather frustrating that the authors did not refer to any of our several contributions on the subject that have been published in recognized books and acknowledged journals (including *Journal of Neurosurgery*) and have been indexed in leading reference databases, including MEDLINE and PubMed.^{1–16} We believe that our articles were the first in the neurosurgery literature to discuss vascularized pedicled flaps based on the temporalis muscle and its fascial layers and to exploit the vascularity of these structures in reconstructing the anterior and middle cranial fossa floors in single and multiple layers.

The authors mentioned that the “subgaleal fascia and the adherent periosteum overlying the skull define the pericranium.” The term “subgaleal fascia” was used by us for the first time in the neurosurgery literature.¹³ The superficial and deep layers of the temporalis fascial, subgaleal fascial, and pericranium layers can be rotated on vascular pedicles of deep and superficial temporal arteries. High vascularity, local availability, ease of harvesting, long length and wide arc of possible rotation, and several such characteristics make temporalis muscle- and fascia-based flaps ideal for basal reconstruction. The number of steps related to harvesting the flap and its rotation have been elaborately discussed by us and others in the literature. The authors discussed the use of such flaps in combination with nasoseptal flaps. Such a combination appears to be a useful addition to previously discussed methods of reconstruction.

Atul Goel, MCh

King Edward VII Memorial Hospital and Seth G.S. Medical College,
Parel, Mumbai, India

References

1. Goel A: Alternative methods for reconstruction of skull base bone using locally available alternatives, in Torrens MJ, Al-Mefty A, Kobayashi S (eds): **Operative Skull Base Surgery**. New York: Churchill Livingstone, 1997, pp 359–372
2. Goel A: Extended vascularized temporalis muscle-fascia flap. **Br J Neurosurg** 8:731–733, 1994
3. Goel A: Long vascular pedicle cranial flap. **Br J Neurosurg** 9:667–670, 1995
4. Goel A: Multilayer reconstruction of anterior cranial fossa floor. **Br J Neurosurg** 12:254–258, 1998
5. Goel A: Multilayer reconstruction of middle fossa floor. **Acta Neurochir (Wien)** 138:584–589, 1996
6. Goel A: Reconstructing the “skull base” divide. **World Neurosurg** 81:54–55, 2014
7. Goel A: Reconstruction of the skull base using locally available alternative: a review. **Indian J Plast Surg** 25:57–62, 1995
8. Goel A: Split-calvaria osteoplastic flap. **J Neurosurg** 82:150–151, 1995 (Letter)
9. Goel A: Use of outer layer of dura as a pedicled flap. **Surg Neurol** 44:92–93, 1995
10. Goel A: Vascularized bone flap for anterior skull base reconstruction. **Acta Neurochir (Wien)** 128:166–168, 1994
11. Goel A: Vascularized osteomyoplastic flaps for skull base reconstruction. **Br J Neurosurg** 8:79–82, 1994
12. Goel A: Vascularized rotational temporal bone flap. **J Neurosurg** 6:281–283, 2016 (Letter)
13. Goel A, Gahankari D: Extended subgaleal fascia-pericranial flap for anterior skull base reconstruction. **Acta Neurochir (Wien)** 135:203–205, 1995
14. Goel A, Gupta S: Reconstruction of skull base: a review of personal techniques. **Neurol India** 48:208–215, 2000
15. Goel A, Muzumdar DP: Reconstruction of the sella floor using vascularized pedicled mucosal flap. **Br J Neurosurg** 17:553–555, 2003
16. Goel A, Nitta J, Kobayashi S, Hongo K: Reconstruction of the skull base, in Kobayashi S, Goel A, Hongo K (eds): **Neurosurgery of Complex Tumours and Vascular Lesions**. New York: Churchill Livingstone, 1997, pp 393–414
17. Safavi-Abbasi S, Komune N, Archer JB, Sun H, Theodore N, James J, et al: Surgical anatomy and utility of pedicled

vascularized tissue flaps for multilayered repair of skull base defects. *J Neurosurg* [epub ahead of print November 27, 2015. DOI: 10.3171/2015.5.JNS15529]

Disclosures

The author reports no conflict of interest.

Response

We are extremely grateful for Dr. Goel's insightful critique of our recently published paper on the surgical anatomy of vascularized flaps. Indeed, the aim of that study was to revisit the anatomy of such flaps and describe their combinations, especially with the more recently utilized nasoseptal flap. In that short, focused paper, we limited our citations on the anatomical properties of such flaps, and we apologize for our failure to cite the important papers described by Dr. Goel.¹⁻¹⁰ We are thankful for his communication as it adds to the discussion of the important topic of the management of skull base lesions.

Sam Safavi-Abbasi, MD, PhD

Robert F. Spetzler, MD

On behalf of all authors

Barrow Neurological Institute, St. Joseph's Hospital and Medical Center,
Phoenix, AZ

References

- Goel A: Extended vascularised temporalis muscle-fascia flap. *Br J Neurosurg* **8**:731-733, 1994
- Goel A: Long vascular pedicle cranial flap. *Br J Neurosurg* **9**:667-670, 1995
- Goel A: Multilayer reconstruction of anterior cranial fossa floor. *Br J Neurosurg* **12**:254-258, 1998
- Goel A: Multilayer reconstruction of middle fossa floor. *Acta Neurochir (Wien)* **138**:584-589, 1996
- Goel A: Reconstruction of the skull base using locally available alternative: a review. *Indian J Plast Surg* **25**:57-62, 1995
- Goel A: Split-calvaria osteoplastic flap. *J Neurosurg* **82**:150-151, 1995 (Letter)
- Goel A: Use of outer layer of dura as a pedicled flap. *Surg Neurol* **44**:92-93, 1995
- Goel A: Vascularised bone flap for anterior skull base reconstruction. *Acta Neurochir (Wien)* **128**:166-168, 1994
- Goel A: Vascularized osteomyoplastic flaps for skull base reconstruction. *Br J Neurosurg* **8**:79-82, 1994
- Goel A, Gahankari D: Extended subgaleal fascia-pericranial flap for anterior skull base reconstruction. *Acta Neurochir (Wien)* **135**:203-205, 1995

INCLUDE WHEN CITING

Published online March 25, 2016; DOI: 10.3171/2015.12.JNS152793.

©AANS, 2016

Surgical management of pituitary macroadenomas

TO THE EDITOR: I read the article by Hoang et al.¹²

with interest (Hoang N, Tran DK, Herde R, et al: Pituitary macroadenomas with oculomotor cistern extension and tracking: implications for surgical management. *J Neurosurg* [epub ahead of print November 13, 2015. DOI: 10.3171/2015.5.JNS15107]). The authors discuss the anatomical extension of pituitary macroadenomas along the roof of the cavernous sinus into the oculomotor cistern and evaluate the clinical and surgical implications. It is unfortunate and rather surprising that the authors did not review the literature on the subject and have ignored my several published articles that concern the relationship of the pituitary macroadenomas to the cavernous sinus and to its "dural" roof and extension of the tumor in the oculomotor cistern.¹⁻¹¹ The authors should have discussed the issues regarding the dura of the diaphragma sellae and of the medial and superior walls of cavernous sinus in the perspective of what is published in the literature rather than presenting the information as an original contribution.

In the year 2004, we presented a classification system for giant pituitary adenomas as per their anatomical extensions, their relationship to the diaphragma sellae, and their relationship to the dural walls of the cavernous sinus.⁹ We believe that our findings enhanced the understanding of the dural relationships of the pituitary tumors and helped to avoid the need for transcranial surgery, which was commonly undertaken previously. As per this classification, Grade I pituitary tumors are those that have enlarged the sella and superiorly elevated the diaphragma sellae but have not transgressed the diaphragma sellae or the medial wall of the cavernous sinus or invaded the confines of the cavernous sinus. Grade II pituitary tumors are those that have invaded the confines of the cavernous sinus by transgressing its "weak" medial wall.³ Encasement of the intracavernous carotid artery is the radiological parameter that indicates cavernous sinus involvement. Grade III pituitary tumors are those wherein the "dural" roof of the cavernous sinus is elevated. We identified that the elevation of the dural roof of the cavernous sinus is a frequent occurrence in large or giant pituitary tumors. We also alluded to the fact that—based on our surgical experience—although the roof of the cavernous is thin, its transgression by pituitary tumors is a rare feature. The elevation of the dural roof of the cavernous sinus gives an impression of a discrete "dot" on axial imaging. The tumor extends into the region of the oculomotor cistern, but a clear dural membrane exists. Understanding the presence of such a dural membrane has surgical implications, as it provides a remarkable plane of dissection from the intracranial structures and, more importantly, from the oculomotor nerve, which has its own defined dural compartment in the superolateral roof of the cavernous sinus.¹⁰ We have elaborately discussed the extension of pituitary tumors into the region of the roof of the cavernous sinus and its relationship with the oculomotor cistern and with the oculomotor nerve. In 1 case shown by the authors (Fig. 1 in their article), the tumor appears to be in the subarachnoid space of the oculomotor cistern, but in all other cases it appears that the roof of the cavernous sinus is elevated and not transgressed by the tumor. Grade IV pituitary tumors are those that have extended into the subarachnoid spaces and encased the arteries of the circle of Willis. The exact site of the dural dehiscence that results

in extension of the pituitary tumors into the subarachnoid space is unclear. The dural roof of the cavernous sinus is “weak,” as the authors have observed, and it is a distinct possibility that dehiscence at this site could allow tumor to extend into the intracranial subarachnoid spaces, although it clearly does not occur often. We have also observed that the Grade III (and also Grade IV) pituitary tumors are biologically of a more aggressive nature, with significantly higher recurrence and growth rates than Grade I and Grade II tumors. Up-front radiation treatment seems to be a viable option in such cases of large or giant pituitary tumors that elevate the roof of the cavernous sinus and extend into the region of the oculomotor cistern.^{5–9,11}

Atul Goel, MCh

King Edward VII Memorial Hospital and Seth G.S. Medical College,
Parel, Mumbai, India

References

- Goel A: Challenge of giant pituitary tumors. **World Neurosurg** 82:e121–e124, 2014
- Goel A: Is the endoscope useful for pituitary tumor surgery?, in Al-Mefty O (ed): **Controversies in Neurosurgery II**. Stuttgart: Thieme, 2013
- Goel A: Medial compartment of the cavernous sinus. **J Neurosurg** 82:763–764, 1995 (Letter)
- Goel A: Transcranial approaches to the sella, suprasellar and parasellar area, in Snyderman C, Gardner P (eds): **Master Techniques in Otolaryngology–Head and Neck Surgery**. Philadelphia: Wolters Kluwer, 2015, pp 37–58
- Goel A, Muzumdar DP: Surgical management of giant pituitary adenomas. **Int Congr Ser** 1259:99–106, 2004
- Goel A, Nadkarni TD: Giant pituitary tumors: a study based on surgical treatment of 180 cases. **Jpn J Neurosurg (Tokyo)** 14:22–35, 2005
- Goel A, Nadkarni TD: Giant pituitary tumors: a study based on surgical treatment of 325 cases. **Int J Neurol Neurosurg** 1:39–52, 2009
- Goel A, Nadkarni TD: Giant pituitary tumors: surgical treatment of 265 cases, in Dolenc VV, Rogers L (eds): **Cavernous Sinus: Developments and Future Perspectives**. Vienna: Springer, 2009, pp 191–204
- Goel A, Nadkarni T, Muzumdar D, Desai K, Phalke U, Sharma P: Giant pituitary tumors: a study based on surgical treatment of 118 cases. **Surg Neurol** 61:436–446, 2004
- Goel A, Shah A: “Interdural” oculomotor neurinoma: report of two surgically treated cases. **Acta Neurochir (Wien)** 152:1721–1724, 2010
- Goel A, Shah A, Jhawar SS, Goel NK: Fluid-fluid level in pituitary tumors: analysis of management of 106 cases. **J Neurosurg** 112:1341–1346, 2010
- Hoang N, Tran DK, Herde R, Couldwell GC, Osborn AG, Couldwell WT: Pituitary macroadenomas with oculomotor cistern extension and tracking: implications for surgical management. **J Neurosurg** [epub ahead of print November 13, 2015. DOI: 10.3171/2015.5.JNS15107]

Disclosures

The author reports no conflict of interest.

Response

We appreciate Dr. Goel’s response and interest in our

report. He has greatly advanced the literature on the extension of giant pituitary adenomas (PAs) and their relationship with the dural membranes.^{7–11} As Dr. Goel described previously, not all giant PAs are alike; in Grades II–IV pituitary tumors, the differences in extension play a critical role in surgical management.^{9,11} The extension of PAs into the wall of the cavernous sinus has been well described.^{1,12,14} Transgression into the medial wall through the soft and friable single layer of dura is commonly observed. The infiltrative process of extension into the venous sinuses results in encasement of the carotid artery, lateral displacement of the cranial nerves, and infiltration and, as we noted in 4% of cases, tracking along the oculomotor cistern into the subarachnoid space.^{11–13} In our report, we wished to show a type of extension that many have observed but that may be underappreciated if a large pituitary adenoma also possesses disproportionately larger suprasellar extension through the superior wall at the region of the oculomotor cistern. This was specifically visualized in all of the cases we discussed.⁶ In Dr. Goel’s description of the classification of giant pituitary tumors,¹¹ we note that there was no specific category for tumors extending through the oculomotor cistern rather than other locations in the superior cavernous sinus wall.

A Grade III tumor in which the roof of the cavernous sinus is merely elevated by the mass, but not transgressed, is less challenging because there is a corridor to access the tumor from below.⁵ A tumor that traverses the oculomotor foramen is important to recognize preoperatively as it renders an approach through the cavernous sinus from the transsphenoidal route problematic.^{3–5}

We do not doubt that there are giant PAs in large series previously reported that have extension through the oculomotor cistern;^{10,11} however, in our paper, we sought to identify the imaging features of the oculomotor foramen tumor growth and its prevalence in these large and invasive tumors as specific preoperative imaging features to recognize these and help guide surgical management. Additionally, we detailed the unique clinical presentation among this subset of patients who present with third cranial nerve palsy outside of the typical presentation of pituitary apoplexy.² All of these features are unique to our study and not specifically addressed in Dr. Goel’s publications on giant adenomas. In our illustrations, we depicted tumors that extend into the subarachnoid space via the oculomotor cistern. We believe that this feature, while uncommon, merits recognition for proper patient counseling and the need for further observation of adjuvant treatment.

William T. Couldwell, MD, PhD
Nguyen Hoang, MD

Clinical Neurosciences Center, University of Utah, Salt Lake City, UT

References

- Campero A, Campero AA, Martins C, Yasuda A, Rhoton AL Jr: Surgical anatomy of the dural walls of the cavernous sinus. **J Clin Neurosci** 17:746–750, 2010
- Cinar N, Tekinel Y, Dagdelen S, Oruckaptan H, Soylemezoglu F, Erbas T: Cavernous sinus invasion might be a risk factor for apoplexy. **Pituitary** 16:483–489, 2013

3. Couldwell W: Craniotomy for suprasellar tumor, in Snyderman C, Gardner PA, Myers EN (eds): **Master Techniques in Otolaryngologic Surgery—Head and Neck Surgery: Skull Base Surgery**. Philadelphia: Lippincott, Williams & Wilkins, 2014
4. Couldwell WT: Transsphenoidal and transcranial surgery for pituitary adenomas. **J Neurooncol** 69:237–256, 2004
5. Couldwell WT, Weiss MH, Rabb C, Liu JK, Apfelbaum RI, Fukushima T: Variations on the standard transsphenoidal approach to the sellar region, with emphasis on the extended approaches and parasellar approaches: surgical experience in 105 cases. **Neurosurgery** 55:539–550, 2004
6. Everton KL, Rassner UA, Osborn AG, Harnsberger HR: The oculomotor cistern: anatomy and high-resolution imaging. **AJNR Am J Neuroradiol** 29:1344–1348, 2008
7. Goel A: Challenge of giant pituitary tumors. **World Neurosurg** 82:e121–e124, 2014
8. Goel A, Muzumdar DP: Surgical management of giant pituitary adenomas. **Int Congress Ser** 1259:99–106, 2004
9. Goel A, Nadkarni T: Medial compartment of the cavernous sinus. **J Neurosurg** 83:763–764, 1995
10. Goel A, Nadkarni T: Surgical management of giant pituitary tumours—a review of 30 cases. **Acta Neurochir** 138:1042–1049, 1996
11. Goel A, Nadkarni T, Muzumdar D, Desai K, Phalke U, Sharma P: Giant pituitary tumors: a study based on surgical treatment of 118 cases. **Surg Neurol** 61:436–446, 2004
12. Micko ASG, Wöhrer A, Wolfsberger S, Knosp E: Invasion of the cavernous sinus space in pituitary adenomas: endoscopic verification and its correlation with an MRI-based classification. **J Neurosurg** 122:803–811, 2015
13. Oldfield EH: Editorial: management of invasion by pituitary adenomas. **J Neurosurg** 121:501–503, 2014
14. Yasuda A, Campero A, Martins C, Rhoton AL Jr, de Oliveira E, Ribas GC: Microsurgical anatomy and approaches to the cavernous sinus. **Neurosurgery** 56 (1 Suppl):4–27, 2005

INCLUDE WHEN CITING

Published online April 8, 2016; DOI: 10.3171/2015.11.JNS152682.

©AANS, 2016

Pregnancy, epilepsy, and glioma survival

TO THE EDITOR: We enjoyed reading the recent paper by Rønning et al.⁵ (Rønning PA, Helseth E, Meling TR, et al: The effect of pregnancy on survival in a low-grade glioma cohort. *J Neurosurg* [epub ahead of print January 1, 2016. DOI: 10.3171/2015.6.JNS15985]). The authors are to be congratulated for this informative, population-based study including patients from 2 large, prospectively maintained registries (Cancer Registry of Norway and Medical Birth Registry of Norway). They performed the largest study to date focused on the impact of pregnancy on survival in patients with low-grade glioma (LGG; 12 WHO Grade I and 53 WHO Grade II) and proposed that pregnancy does not seem to have an impact on the survival of female patients with LGG.

Given the findings from our own clinical practice, we enthusiastically support all data allowing better counseling of women harboring a glioma and envisioning a pregnan-

cy or women with a glioma discovered during pregnancy. Rønning et al. report encouraging results supporting the absence of a survival impact in pregnant women with LGG. However, their final statement as regards the counseling of female patients with LGG that “pregnancy does not seem to influence their overall survival” sounds overly optimistic and should be restricted to indicate simply that the present results showed no negative impact of pregnancy on overall survival in LGG, which is an important and novel finding. Indeed, the authors’ population-based study contains an inevitable bias in the group definition as LGG aggressiveness and evolution possibly interact with the choice of being or not being pregnant. Thus, the pregnancies possibly occurred in “low-risk LGG” patients, a factor that the present study is unable to identify (note that there is no information regarding tumor size, location, functional status, extent of resection, molecular markers, or detailed oncological treatment). Patients who did not deliver may have had worsening of their LGG, as supported by their higher proportion of adjuvant therapies (chemotherapy 10.3% vs 1.5%, radiotherapy 24.6% vs 9.2%). In contrast, patients who gave birth were in good clinical condition and possibly maintained control of their LGG, as supported by a younger age (25.3 vs 31.4 years), by an increased overall survival, and by parity after an LGG diagnosis.

Moreover, the prognostic significance of epilepsy on LGG survival cannot be drawn from the present results as the authors apparently studied the rate of “epilepsy during pregnancy,” not the rate of “epilepsy at LGG diagnosis.” The discussion should ideally suggest that “we did not observe any statistically significant effect of epilepsy [during pregnancy] as a prognostic factor” and that “we believe the prognostic effects of epilepsy during pregnancy to be modest, if present at all.” To be more precise, a history of epileptic seizures at diagnosis has been identified as a strong, independent, protective prognostic parameter for malignant transformation and for overall survival in the largest series ever published regarding epileptic seizures in 1509 adults with supratentorial WHO Grade II gliomas.²

Finally, this quality study questions why the transient clinical and imaging deteriorations we observe during pregnancy, in both Grade I and II gliomas, do not systematically translate into worsened long-term evolution, even though malignant transformation has been reported.^{1,3,4,6,7}

Johan Pallud, MD, PhD
Sophie Peeters, BA

Sainte-Anne Hospital, Paris, France
University Paris Descartes, Paris, France

References

1. Knafo S, Goutagny S, Pallud J: Increased growth rate of a WHO grade I ganglioglioma during pregnancy. **Br J Neurosurg** 27:119–121, 2013
2. Pallud J, Audureau E, Blonski M, Sanai N, Bauchet L, Fontaine D, et al: Epileptic seizures in diffuse low-grade gliomas in adults. **Brain** 137:449–462, 2014
3. Pallud J, Duffau H, Razak RA, Barbarino-Monnier P, Capelle

- L, Fontaine D, et al: Influence of pregnancy in the behavior of diffuse gliomas: clinical cases of a French glioma study group. *J Neurol* **256**:2014–2020, 2009
4. Pallud J, Mandonnet E, Deroulers C, Fontaine D, Badoual M, Capelle L, et al: Pregnancy increases the growth rates of World Health Organization grade II gliomas. *Ann Neurol* **67**:398–404, 2010
 5. Rønning PA, Helseth E, Meling TR, Johannesen TB: The effect of pregnancy on survival in a low-grade glioma cohort. *J Neurosurg* [epub ahead of print January 1, 2016. DOI: 10.3171/2015.6.JNS15985]
 6. Yust-Katz S, de Groot JF, Liu D, Wu J, Yuan Y, Anderson MD, et al: Pregnancy and glial brain tumors. *Neuro Oncol* **16**:1289–1294, 2014
 7. Zwinkels H, Dörr J, Kloet F, Taphoorn MJB, Vecht CJ: Pregnancy in women with gliomas: a case-series and review of the literature. *J Neurooncol* **115**:293–301, 2013

Disclosures

The authors report no conflict of interest.

Response

We thank Dr. Pallud and Ms. Peeters for their thoughtful comments on our article. The issue of pregnancy in patients with LGG is difficult to study given that LGG is a rare disease and that pregnancies in patients with LGG are even rarer. Hence, untangling the prognostic effect of pregnancy is challenging. Moreover, the prospect of obtaining definite proof would require a randomized controlled trial randomizing patients to either pregnancy or no pregnancy, which is untenable for obvious ethical reasons. Thus, we are left with observational data to answer and guide our patients on the topic of pregnancy.

We concede that a possible explanation for our findings and our conclusion of a negligible effect of pregnancy is a selection bias toward pregnancies only in patients with “low-risk LGG.” Unfortunately, the data in the Norwegian cancer registry (CRN) are insufficiently detailed with regard to currently well-established prognostic factors (tumor size, location, extent of resection, molecular markers, and so forth), and we are unable to access these data in retrospect.

Historically, however, many of these prognostic factors for LGG were not identified and universally accepted at the time of diagnosis; consequently, we doubt whether any clinician at the time of diagnosis would have classified them as low-risk or high-risk LGG. From a theoretical standpoint, since the data are observational and not randomized, one could also hypothesize that pregnancy itself could impede the growth and/or transformation of the LGG and thus explain the lower rates of chemotherapy and radiotherapy utilized.

Pallud and Peeters claim that we studied the rate of “epilepsy during pregnancy” and not the rate of “epilepsy at LGG diagnosis.” We respectfully disagree. In Norway, upon confirmation of pregnancy, the general practitioner or midwife completes a primary notification of pregnancy. This notification includes a tick mark for prior epilepsy including specification of any antiepileptic medication. Upon delivery of a child, the midwife completes a new notification based on the primary notification that also includes information on any new health issues arising during preg-

nancy (http://www.fhi.no/eway/default.aspx?pid=240&trg=Main_6664&Main_6664=6898:0:25,7840:1:0:0::0:0). Our analysis was based on information regarding prior epilepsy. Thus, we maintain that we studied the rate of epilepsy at diagnosis. We are well aware that this is at odds with the findings by Pallud et al.² However, corresponding to our findings are data in a cohort of 379 Norwegian LGG patients in whom epilepsy was not found to be a significant prognostic factor.¹

We admit that our data do not tell the whole story, but given the dearth of pregnant LGG patients we must base our patient recommendations on the best available evidence. To our knowledge, this is the largest cohort of pregnant LGG patients described, and we failed to identify pregnancy as a detrimental prognostic factor. Thus, in the future, we will counsel our female LGG patients that pregnancy in itself has not been documented to worsen prognosis. However, the patient will also be informed about the uncertainties pertaining to this issue and that she must be cognizant of the overall reduced expected survival from the LGG.

We welcome all international collaboration on the issue of pregnancy in LGG patients because it can only be resolved with a larger number of observations due to the ethical concerns prohibiting definitive certainty.

Pål A. Rønning, MD

Eirik Helseth, MD, PhD

Torstein R. Meling, MD, PhD

Oslo University Hospital, Oslo, Norway

Tom B. Johannesen, MD, PhD

Cancer Registry of Norway, Oslo, Norway

References

1. Lote K, Egeland T, Hager B, Stenwig B, Skullerud K, Berg-Johnsen J, et al: Survival, prognostic factors, and therapeutic efficacy in low-grade glioma: a retrospective study in 379 patients. *J Clin Oncol* **15**:3129–3140, 1997
2. Pallud J, Audureau E, Blonski M, Sanai N, Bauchet L, Fontaine D, et al: Epileptic seizures in diffuse low-grade gliomas in adults. *Brain* **137**:449–462, 2014

INCLUDE WHEN CITING

Published online May 13, 2016; DOI: 10.3171/2016.1.JNS16119.

©AANS, 2016

Biases in estimation of overall survival in patients who underwent repeat resection of glioblastoma

TO THE EDITOR: We read with great interest the articles by Bloch et al.² (Bloch O, Han SJ, Cha S, et al: Impact of extent of resection for recurrent glioblastoma on overall survival. *J Neurosurg* **117**:1032–1038, December 2012) and Chaichana et al.³ (Chaichana KL, Zadnik P, Weingart JD, et al: Multiple resections for patients with glio-

FIG. 1. Figures 2 (left) and 3 (right) from Chaichana et al. Circles with arrows were placed to illustrate the plateau in the survival curve created by biases in the OS calculation. Modified with permission from the American Association of Neurological Surgeons.

blastoma: prolonging survival. *J Neurosurg* 118:812–820, April 2013). Similar flaws pertaining to the analysis performed in both manuscripts led us to question the conclusions drawn.

Bloch et al. conclude that extent of resection (EOR) at recurrence is an independent predictor of overall survival (OS), regardless of the status of initial EOR. However, in the univariate and multivariate OS analyses (see Figs. 2 and 3 and Table 4 in Bloch et al.), time of diagnosis serves as the starting time (T_0) for calculating survival. Because the EOR and Karnofsky Performance Scale (KPS) score were measured at second resection and were not known at the time of diagnosis, stratifying by these factors at the time of diagnosis is incorrect and can lead to bias in interpretation of results. As noted in the highly regarded and cited work by Anderson et al.,¹ stratifying by treatment response and treating patients as at risk of death before

response assessment may inappropriately bias the results in favor of treatment responders (in this case patients with gross-total resection [GTR]), and inappropriately assign an unfavorable survival for treatment nonresponders (patients with subtotal resection [STR]).

Similarly, in the article by Chaichana et al., the authors conclude that patients with glioblastoma (GBM) demonstrated improved survival with repeated resections. Patients need to live long enough to undergo repeat resections, which creates an inherent bias in estimating OS. This bias is clearly demonstrated in Fig. 2 of their work, with the initial plateau of survival curves for patients with multiple resections, and is shown quite strongly for patients who had 4 resections (Fig. 1 left). A plateau can also be seen for patients who had 2 resections in Fig. 3 from Chaichana et al. (Fig. 1 right), and similarly for Fig. 3 from Bloch et al. (Fig. 2). In the discussion, Chaichana et al. argue that this

FIG. 2. Figure 3 from Bloch et al. Circles with arrows were placed to illustrate the plateau in the survival curve created by biases in the OS calculation. Modified with permission from the American Association of Neurological Surgeons.

bias is accounted for by performing multivariate analysis, case-control analysis, and excluding patients with incomplete information. However, these methods are insufficient because they do not account for the bias in OS estimation.

Appropriate statistical methods exist to account for the bias in OS estimation in favor of patients who were alive and able to undergo treatment, including the following: 1) starting the clock at repeat resection; or 2) treating variables measured at repeat resection, including EOR or occurrence of repeat resection, as time-dependent covariates.

The conclusions in both papers suggest that repeat resection is independently beneficial for the patient, which impacts the financial burden on the patients, insurance companies, and taxpayers, and also creates the potential for additional surgical complications and reduction in quality of life for patients. We encourage the authors to reanalyze the data using appropriate statistical methods to ensure that repeat surgeries are truly beneficial for patients' OS.

Debra A. Goldman, MS

Katherine S. Panageas, DrPH

Memorial Sloan Kettering Cancer Center, New York, NY

References

1. Anderson JR, Cain KC, Gelber RD: Analysis of survival by tumor response. *J Clin Oncol* **1**:710–719, 1983
2. Bloch O, Han SJ, Cha S, Sun MZ, Aghi MK, McDermott MW, et al: Impact of extent of resection for recurrent glioblastoma on overall survival. *J Neurosurg* **117**:1032–1038, 2012
3. Chaichana KL, Zadnik P, Weingart JD, Olivi A, Gallia GL, Blakeley J, et al: Multiple resections for patients with glioblastoma: prolonging survival. *J Neurosurg* **118**:812–820, 2013

Disclosures

The authors report no conflict of interest.

Response

We thank Ms. Goldman and Dr. Panageas for their interest and comments regarding our study. They have raised concerns regarding statistical methods employed in the manuscript, specifically with regard to univariate and multivariate survival analyses stratified by EOR. They claim that stratification by treatment response inherently biases the outcomes of the group with the better response. Although we agree with this point in principle, we believe that they have misinterpreted the role of EOR assessment in this study. The EOR is not a measure of treatment response, but rather the treatment itself. For these patients, surgery is a major part of the overall treatment, and comparison of patients receiving GTR versus STR is equivalent to a study comparing resection versus biopsy, or surgical versus medical treatment alone. Unlike in other cancers in which response is measured by total disease burden, treatment response in GBM is measured primarily by progression (using Response Assessment in Neuro-On-

cology [RANO] criteria) and death. Their suggestion that stratifying by groups for comparison by EOR at second resection introduced bias presupposes that EOR impacts survival. This is, in fact, the central question of the study, but it had not been previously demonstrated with data for second resection and cannot be assumed. We do agree that EOR at initial resection has been demonstrated to impact survival in numerous retrospective studies, which is why patients were first stratified by initial EOR and then compared independently within each stratum for the impact of EOR at second resection (see Fig. 3 in our original article).

The correspondents also comment on the inherent bias of the study that only includes patients who were healthy enough to have 2 resections of their GBM. They point out an initial plateau in the Kaplan-Meier curves corresponding to the uniform survival of patients from the first to second resection. We fully acknowledge that this is a limitation of our retrospective study and have addressed this issue specifically in the discussion. The study is not meant to suggest that all patients should have 2 or more resections of their GBM. We know that many patients will not have a performance status adequate enough to undergo a second resection at progression or will not have tumors amenable to surgery. However, just as prior studies of the impact of initial EOR on survival have led to guidelines for the treatment of newly diagnosed GBM—guidelines that suggest that “maximal safe surgical resection” should be attempted when appropriate—we hope that data on the survival impact of EOR at re-resection influences surgical decision making at reoperation. Since the original publication of this manuscript in 2012, significant advances in preoperative functional imaging, intraoperative navigation, and electrophysiological monitoring now allow aggressive surgery to be safer than ever. We hope that the message taken from our study is that if a patient is a good candidate for repeat resection of a GBM for cytoreductive, mass relief, or tissue diagnostic purposes, then the goal of surgery should be as complete a resection as safely possible. We believe the data strongly suggest that this approach may improve OS.

Orin Bloch, MD

Northwestern University, Chicago, IL

Seunggu J. Han, MD

Soonmee Cha, MD

Manish K. Aghi, MD, PhD

Michael W. McDermott, MD

Mitchel S. Berger, MD

University of California San Francisco, San Francisco, CA

Matthew Z. Sun, MD

University of California Los Angeles, Los Angeles, CA

Response

Surgery can have a positive impact on the outcomes for patients with GBM, in whom more extensive resections without iatrogenic deficits can prolong survival and delay recurrence.^{3,4,8–10} However, patients with GBM, regardless of EOR (including supratotal resection), will invariably

have tumor recurrence.⁷ The question is whether there is a role for repeat surgery in prolonging survival. In our article titled "Multiple resections for patients with glioblastoma: prolonging survival," we performed a retrospective study in 578 patients who underwent surgery at a single tertiary care institution for a primary GBM between 1997 and 2007. Of these individuals, 354, 168, 41, and 15 patients underwent 1, 2, 3, or 4 resections, respectively. The median survival was 6.8, 15.5, 22.4, and 26.6 months for patients with each successive increase in number of resections. To attempt to minimize biases, a case-control evaluation was also done, in which groups were matched for factors known to be associated with outcomes, including age, preoperative neurological function, periventricular tumor location, EOR, and adjuvant therapy among resection groups.^{1,2,4-6} In this case-control analysis, patients with an increasing number of resections had significantly increased survival; patients with 1, 2, and 3 resections had a median survival of 4.5, 16.2, and 24.4 months, respectively. This raises the possibility that maximal resection on each recurrence plays an important role in prolonging OS.

We appreciate the letter by Goldman and Panageas about our study. In their letter to the editor, they raise the concern of when to designate the starting time (T_0) for survival calculation. In our study, and in a similar one by Bloch et al., T_0 was designated at the time of tissue diagnosis, which corresponded to the date of the first surgery. We opted to designate this as T_0 to evaluate whether repeat surgery could prolong survival from the time of initial diagnosis. If T_0 started at each successive surgery, then it would not accurately capture the time the patient has survived in relation to the surgery number. Goldman and Panageas argue that such a designation introduces biases because patients need to live long enough to undergo repeat resections. One possibility is that patients continue to live longer due to each of the resections done for maximal resection of cancer. The bias pointed out by their letter may be present, and that is precisely why we designed our study the way we did. We aimed to minimize such a bias by performing a case-control study among patients with 1, 2, and 3 resections, in which groups were matched by factors known to be associated with outcome (age, preoperative neurological function, periventricular tumor location, EOR, and adjuvant therapy).^{1,2,4-6} However, given that this was a retrospective study, it would not be possible to eliminate this bias altogether regardless of the statistical method used to analyze the data.

Clinical studies, especially surgically based studies such as this one, in which patients continue to have GBM recurrence despite maximal resections each time, and continue to have a good KPS score, are challenging to perform in a randomized controlled manner. A randomized controlled study would provide the highest-quality information on whether recurrent surgery could prolong survival, but then one has to raise the issue with patients to determine whether or not this is ethically possible. As such, given its retrospective nature, we aimed to use the data we had from our institution: a large number of patients at a single center where there is a group of subspecialized brain tumor surgeons, and where patients are treated by the same group of oncologists. We further used the statistical methods avail-

able to minimize these biases, to provide the best information possible regarding whether repeat surgery can prolong survival. Our study demonstrates that patients who undergo repeat resection may have an increased survival benefit, and that these resections can occur with no increase in morbidity and/or mortality. Despite the potential sources of biases, these findings can help provide insight into the management of patients with recurrent GBM, and as long as the surgeries are done in high-volume centers with subspecialized care, the potential for additional surgical complications has been negligible in studies like ours, and the impact on the quality of life of the patients has been very positive in our experience.

Kaisorn L. Chaichana, MD
Alfredo Quinones-Hinojosa, MD
Johns Hopkins University, Baltimore, MD

References

1. Chaichana K, Parker S, Olivi A, Quiñones-Hinojosa A: A proposed classification system that projects outcomes based on preoperative variables for adult patients with glioblastoma multiforme. *J Neurosurg* **112**:997-1004, 2010
2. Chaichana KL, Cabrera-Aldana EE, Jusue-Torres I, Wijesekera O, Olivi A, Rahman M, et al: When gross total resection of a glioblastoma is possible, how much resection should be achieved? *World Neurosurg* **82**:e257-e265, 2014
3. Chaichana KL, Garzon-Muvdi T, Parker S, Weingart JD, Olivi A, Bennett R, et al: Supratentorial glioblastoma multiforme: the role of surgical resection versus biopsy among older patients. *Ann Surg Oncol* **18**:239-245, 2011
4. Chaichana KL, Jusue-Torres I, Navarro-Ramirez R, Raza SM, Pascual-Gallego M, Ibrahim A, et al: Establishing percent resection and residual volume thresholds affecting survival and recurrence for patients with newly diagnosed intracranial glioblastoma. *Neuro Oncol* **16**:113-122, 2014
5. Chaichana KL, Pendleton C, Chambless L, Camara-Quintana J, Nathan JK, Hassam-Malani L, et al: Multi-institutional validation of a preoperative scoring system which predicts survival for patients with glioblastoma. *J Clin Neurosci* **20**:1422-1426, 2013
6. Chaichana KL, Zaidi H, Pendleton C, McGirt MJ, Grossman R, Weingart JD, et al: The efficacy of carmustine wafers for older patients with glioblastoma multiforme: prolonging survival. *Neurol Res* **33**:759-764, 2011
7. Dandy WE: Removal of right cerebral hemisphere for certain tumors with hemiplegia. *J Am Med Assoc* **90**:823-825, 1928
8. Lacroix M, Abi-Said D, Fourney DR, Gokaslan ZL, Shi W, DeMonte F, et al: A multivariate analysis of 416 patients with glioblastoma multiforme: prognosis, extent of resection, and survival. *J Neurosurg* **95**:190-198, 2001
9. McGirt MJ, Chaichana KL, Gathinji M, Attenello FJ, Than K, Olivi A, et al: Independent association of extent of resection with survival in patients with malignant brain astrocytoma. *J Neurosurg* **110**:156-162, 2009
10. Sanai N, Polley MY, McDermott MW, Parsa AT, Berger MS: An extent of resection threshold for newly diagnosed glioblastomas. *J Neurosurg* **115**:3-8, 2011

INCLUDE WHEN CITING

Published online June 3, 2016; DOI: 10.3171/2015.11.JNS152515.

©AANS, 2016

Does physician specialty really matter?

TO THE EDITOR: We read with great interest the article by Fennell et al.¹ (Fennell VS, Martirosyan NL, Palejwala SK, et al: Morbidity and mortality of patients with endovascularly treated intracerebral aneurysms: does physician specialty matter? *J Neurosurg* 124:13–17, January 2016). The authors are to be applauded for their efforts to sort out issues related to outcomes following endovascular intervention. This article and the 2 accompanying commentaries and responses point out the limitations of their study and call for standardizing training and reporting as means to assure and improve quality. Meyer et al. specifically noted that the Society of Neurological Surgery (SNS), via its Committee on Advanced Specialty Training (CAST), has established criteria for accrediting training programs and certifying individuals in neuroendovascular surgery.² None of the manuscripts mention the contributions of the Neuropoint Alliance, Inc. (NPA), a neurosurgical organization created in 2009 to establish registries for gathering and analyzing outcomes data. Given the passionate editorials and responses accompanying this article, we thought it important to make readers aware of the roles that CAST and the NPA can play in addressing the issues brought forth by the articles and ultimately improving patient care.

CAST is charged by the SNS with accrediting enfolded and postresidency neurosurgical subspecialty fellowships and certifying individual trainees in *some* of these subspecialties. For neurosurgeons, this certification is being done in collaboration with the American Board of Neurological Surgery (ABNS). For other specialties (neurology, neuroradiology, others), CAST has linked its certification to active maintenance of the requirements of their primary and subspecialty certifying boards (i.e., American Board of Radiology and American Board of Psychiatry and Neurology).

A Neuroendovascular Surgery Advisory Committee (NESAC), composed of subspecialists from neurosurgery, neurology, and neuroradiology, has assisted CAST in the development of standardized training requirements for neuroendovascular training. After lengthy deliberations, these requirements have been approved by the American Society of Interventional and Therapeutic Neuroradiology (ASITN), the Cerebrovascular Section of the American Association of Neurological Surgeons (AANS) and the Congress of Neurological Surgeons (CNS), and the Society for Neurointerventional Surgery (SNIS). The criteria for program accreditation and individual certification will soon be published in detail.

Each accredited fellowship must be part of or closely associated with a neurosurgical residency accredited by the Accreditation Council of Graduate Medical Education (ACGME), must have at least 2 neuroendovascular faculty members, and must perform 250 or more neuroendovascular cases per year.

Regarding certification of trainees in endovascular neurosurgery:

1. Neurologists and radiologists must have completed a vascular neurology fellowship or neuroradiology fellowship, respectively, and have demonstrated significant critical care exposure. Neurosurgery candidates for fellowship may enfold some or all of their fellowship training within the 7-year neurosurgery residency.
2. Before beginning the year of dedicated endovascular fellowship training, all candidates must have performed 200 diagnostic cerebral angiograms, be competent in their performance, and be knowledgeable in radiation safety and the interpretation of the studies.
3. Each trainee must then spend at least 12 months of dedicated neurointerventional clinical service during which at least 250 interventional cases are performed, to be completed after the prerequisites are met.

Currently, there are 14 CAST-accredited training programs in neuroendovascular surgery; many more are preparing their applications. CAST has recently moved forward with the certification of individuals meeting these requirements, and the first CAST certificates are now under consideration by NESAC and CAST. This first group of individuals must have a validated practice track including completion of pre-CAST endovascular training combined with demonstrated clinical competency and experience in neuroendovascular procedures. Over the next few years, the practice track will close, and only those individuals trained in CAST-accredited programs will thereafter be eligible for CAST certification in this specialty.

Standardization of training would have little value if the quality of the programs, faculty, and the graduates were not assessed. Accordingly, CAST requires patient outcomes data to be recorded in an approved database. NPA, a not-for-profit corporation governed by a board of directors appointed by the AANS, ABNS, SNS and CNS, has created one such database as part of its National Neurosurgical Quality Outcomes Database (N²QOD) program. At present, N²QOD offers a national clinical registry for spine and vascular procedures. Its primary purpose is to document and improve the quality of care for these procedures by providing individual surgeons, practice groups, and hospitals an infrastructure to allow collection, analysis, and feedback of their outcomes with comparison to the universal data set.

Neurosurgeons, neuroradiologists, and vascular neurologists recognize the issues raised by the data reported by Fennell et al. The means to address these issues is by implementing rigorous and standardized accreditation and certification criteria, and by creating the infrastructure for outcome data reporting. The creation of CAST and the NPA will help assure that every endovascular surgeon, regardless of primary specialty background, will maximize his or her patient outcome as a result of superior training and data analysis.

Scott D. Simon, MD

Robert E. Harbaugh, MD

Penn State Hershey Medical Center, Hershey, PA

Arthur L. Day, MD

Memorial Hermann Mischer Neuroscience Institute, Houston, TX

References

1. Fennell VS, Martirosyan NL, Palejwala SK, Lemole GM Jr, Dumont TM: Morbidity and mortality of patients with endovascularly treated intracerebral aneurysms: does physician specialty matter? **J Neurosurg** 124:13–17, 2016
2. Meyers PM, Higashida RT, McDougall CG, Hussein MS, Hirsch JA, Rasmussen RA: Editorial. Discipline and training. **J Neurosurg** 124:9–11, 2016

Disclosures

The authors report no conflict of interest.

Response

We thank the authors for informing us and the readers about the new criteria for standardization in neuroendovascular training. We look forward to the specifications that will be set forth by the NESAC in conjunction with the SNS, via CAST, regarding the requirements of both individual certification and program accreditation. We are also pleased that the ASITN, the joint Cerebrovascular

Section of the AANS and the CNS, and the SNIS are in agreement with the new training requirements.

We share the hope that every endovascular surgeon, regardless of primary specialty, be able to provide reliable patient care. Nevertheless, inherent discrepancies in pre-fellowship training will persist beyond fellowship training, and we thus endorse a multidisciplinary approach in the management of intracerebral aneurysm along with fellowship standardization.

Sheri K. Palejwala, MD

Travis M. Dumont, MD

Banner University Medical Center–Tucson Campus, University of Arizona
College of Medicine, Tucson, AZ

INCLUDE WHEN CITING

Published online June 10, 2016; DOI: 10.3171/2016.3.JNS16721.

©AANS, 2016