Neurosurgical Forum LETTERS TO THE EDITOR

Upfront GKS for Cushing's disease and acromegaly: is it suitable?

TO THE EDITOR: We read with great interest the recent article by Gupta et al.³ (Gupta A, Xu Z, Kano H, et al: Upfront Gamma Knife radiosurgery for Cushing's disease and acromegaly: a multicenter, international study. *J Neurosurg* [epub ahead of print August 17, 2018. DOI: 10.3171/2018.3.JNS18110]). The authors included 21 patients with Cushing's disease (CD) and 25 patients with acromegaly undergoing upfront Gamma Knife radiosurgery (GKS). After a median endocrine follow-up of 69.5 months, patients with CD achieved a faster and far better remission rate compared to patients with acromegaly. The authors suggest a possible differential radiosensitivity of two kinds, and then further recommend upfront GKS in CD rather than in acromegaly. We commend the efforts of the authors in carrying out this interesting study. Yet from the perspective of neurosurgeons, some conclusions are questionable.

The biggest concern lies in the posttreatment remission criteria for CD that were used in this study. The authors defined remission as normalization of urinary free cortisol and morning serum cortisol levels, which is not recognized by most endocrinologists and neurosurgeons. According to the latest Endocrine Society Clinical Practice Guideline for CD, as well as other previous literature, remission is generally defined as morning serum cortisol values < 5 µg/dl, a stricter criterion than just normal range.^{2,5,7} One meta-analysis suggests that patients with CD in whom subnormal cortisol levels are found after treatment have a clearly lower risk of long-term recurrence compared to those within the normal range.⁸ The reduction of cortisol levels to the normal range after treatment does not necessarily represent the patient's cure, but rather a higher recurrence rate.⁹ Regarding this condition as remission could give patients overly optimistic and misleading expectations, and may cause neglect of follow-up. Moreover, the use of different remission criteria hinders direct comparison of outcomes between this GKS study and other surgical treatment studies for CD.

Nevertheless, although the authors have used more easily achievable remission criteria for CD, the remission criteria for acromegaly (i.e., growth hormone [GH] level < 1 ng/ml in response to a glucose challenge) are much stricter and in accordance with the latest guideline.⁴ These

varying degrees of rigor in criteria to assess CD and acromegaly may also make less convincing the conclusion that patients with CD achieve faster and better remission rates and that their disease is more sensitive to GKS than is the case in those with acromegaly.

In addition, this study did not mention the impact of radiotherapy on the growth of younger patients, especially when the youngest patient with CD included in this study was 14 years old. A radiotherapy study in pediatric CD reported that the incidence of GH deficiency after radiation therapy was 36%–68%, and most patients failed to reach the target height.¹ In one study from the Mayo Clinic the investigators also believe that the risk of delayed hypopituitarism caused by radiotherapy is significant.⁶ The risk of this hypopituitarism exists for a lifetime.⁹ It is therefore recommended that this article add age factors when deriving the conclusion of efficacy for upfront GKS for CD and acromegaly treatment. Especially given the lack of long-term follow-up data, the conclusions should be more cautious for the sake of safety.

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References

1. Acharya SV, Gopal RA, Goerge J, Menon PS, Bandgar TR, Shah NS: Radiotherapy in paediatric Cushing's disease: efficacy and long term follow up of pituitary function. *Pituitary* 13:293–297, 2010
2. Bansal P, Lila A, Goroshi M, Jadhav S, Lomte N, Thakkar K, et al: Duration of post-operative hypocortisolism predicts sustained remission after pituitary surgery for Cushing's disease. *Endocr Connect* 6:625–636, 2017
3. Gupta A, Xu Z, Kano H, Sisterson N, Su YH, Krsek M, et al: Upfront Gamma Knife radiosurgery for Cushing's disease and acromegaly: a multicenter, international study. *J Neurosurg* [epub ahead of print August 17, 2018. DOI: 10.3171/2018.3.JNS18110]
4. Katznelson L, Laws ER Jr, Melmed S, Molitch ME, Murad MH, Utz A, et al: Acromegaly: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 99:3933–3951, 2014
5. Nieman LK, Biller BM, Findling JW, Murad MH, Newell-

- Price J, Savage MO, et al: Treatment of Cushing's syndrome: an Endocrine Society clinical practice guideline. **J Clin Endocrinol Metab** **100**:2807–2831, 2015
6. Porterfield JR, Thompson GB, Young WF Jr, Chow JT, Fryrear RS, van Heerden JA, et al: Surgery for Cushing's syndrome: an historical review and recent ten-year experience. **World J Surg** **32**:659–677, 2008
 7. Savage MO, Chan LF, Grossman AB, Storr HL: Work-up and management of paediatric Cushing's syndrome. **Curr Opin Endocrinol Diabetes Obes** **15**:346–351, 2008
 8. Sughrue ME, Shah JK, Devin JK, Kunwar S, Blevins LS Jr: Utility of the immediate postoperative cortisol concentrations in patients with Cushing's disease. **Neurosurgery** **67**:688–695, 2010
 9. Tritos NA, Biller BM, Swearingen B: Management of Cushing disease. **Nat Rev Endocrinol** **7**:279–289, 2011

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Response

We thank Drs. Gao and Xing for their interest in our recent international, multicenter study. In this study, we demonstrated the rates of tumor control and endocrine remission in selected patients with CD and acromegaly who were treated with upfront GKS. The current study cohorts represent a small subset of patients published in our previous studies.^{2,6} Previous series provide evidence that radiosurgery appears to achieve more rapid remission than fractionated radiotherapy.⁵ Among functioning pituitary adenomas, there is evidence to support differences in radiosurgical sensitivity in secretory adenomas, as measured by hormone release.⁹

The authors raise the issue of contemporary definitions of endocrine remission. Endocrine criteria for remission of CD and acromegaly have changed substantially over the 2.5 decades during which our study cohort was accrued. Although applying modern endocrine assays and definitions would be ideal, the approach would be impractical for such a clinical study, and its absence does not negate the significant findings of our study. Not surprisingly, this limitation also holds true for the largest surgical series of pituitary surgery for functioning adenomas.^{3,4} Moreover, given past experiences, the remission criteria and neuroendocrine assay technology are almost certain to be refined in the future. Thus, the remission criteria will remain a moving target.

Latent effects of radiotherapy are not the same in breadth or frequency as those experienced with GKS. For instance, in the CD and acromegaly studies by our group, as well as a review of the literature, we have not seen a single instance of symptomatic carotid stenosis leading to cerebral ischemia.^{2,6,7} This sharply contrasts with radiotherapy series for patients with pituitary adenoma.¹ The same is true for radiation-induced neoplasia and neurocognitive deficits after radiosurgery as compared with radiotherapy for tumors of the sella.^{7,8} Nevertheless, one should always

weigh the benefit-to-risk profile of GKS with those of other treatment options and take into account the natural history of the underlying disease state. For pituitary adenomas, the long-term consequences of action or inaction must be carefully considered.

A large, multicenter, prospective study of patients with pituitary adenomas would probably take at least 5 years from the accrual of patients for intermediate results to be meaningful and more than a decade for long-term results. Furthermore, such an undertaking would require hundreds of patients and millions of dollars to achieve study validity. During that time, it is likely that the study would be confounded by changing technologies (e.g., radiosurgery devices, radiology sequencing, endocrine assays), evolving medical and microsurgical approaches, varied treatment paradigms, and potentially changing criteria for endocrine remission. Until then, the pituitary adenoma radiosurgery studies by the International Radiosurgery Research Foundation (IRRF) will probably remain the highest level of evidence available to guide clinicians.^{2,6}

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References

1. Brada M, Burchell L, Ashley S, Traish D: The incidence of cerebrovascular accidents in patients with pituitary adenoma. **Int J Radiat Oncol Biol Phys** **45**:693–698, 1999
2. Ding D, Mehta GU, Patibandla MR, Lee CC, Liscak R, Kano H, et al: Stereotactic radiosurgery for acromegaly: an international multicenter retrospective cohort study. **Neurosurgery** [epub ahead of print], 2018
3. Hofmann BM, Hlavac M, Martinez R, Buchfelder M, Müller OA, Fahlbusch R: Long-term results after microsurgery for Cushing disease: experience with 426 primary operations over 35 years. **J Neurosurg** **108**:9–18, 2008
4. Jagannathan J, Smith R, DeVroom HL, Vortmeyer AO, Stratakis CA, Nieman LK, et al: Outcome of using the histological pseudocapsule as a surgical capsule in Cushing disease. **J Neurosurg** **111**:531–539, 2009
5. Loeffler JS, Shih HA: Radiation therapy in the management of pituitary adenomas. **J Clin Endocrinol Metab** **96**:1992–2003, 2011
6. Mehta GU, Ding D, Patibandla MR, Kano H, Sisterson N, Su YH, et al: Stereotactic radiosurgery for Cushing disease: results of an international, multicenter study. **J Clin Endocrinol Metab** **102**:4284–4291, 2017
7. Sheehan JP, Niranjan A, Sheehan JM, Jane JA Jr, Laws ER, Kondziolka D, et al: Stereotactic radiosurgery for pituitary adenomas: an intermediate review of its safety, efficacy, and role in the neurosurgical treatment armamentarium. **J Neurosurg** **102**:678–691, 2005
8. Tooze A, Hiles CL, Sheehan JP: Neurocognitive changes in pituitary adenoma patients after gamma knife radiosurgery: a preliminary study. **World Neurosurg** **78**:122–128, 2012
9. Trifiletti DM, Xu Z, Dutta SW, Quiñones-Hinojosa A,

Peterson J, Vance ML, et al: Endocrine remission after pituitary stereotactic radiosurgery: differences in rates of response for matched cohorts of Cushing disease and acromegaly patients. *Int J Radiat Oncol Biol Phys* 101:610–617, 2018

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Inter-rater agreement: a methodological issue

TO THE EDITOR: We read with interest the article by Rinaldo et al.⁴ (Rinaldo L, Johnson DM, Vine RL, et al: Differences between patient- and professional-reported modified Rankin Scale score in patients with unruptured aneurysms. *J Neurosurg* [epub ahead of print August 10, 2018. DOI: 10.3171/2018.3.JNS18247]). The aim of the authors was to compare patient- and nurse-reported modified Rankin Scale (mRS) scores in a consecutive series of patients with unruptured intracranial aneurysm (UIA). A nurse assigned an mRS grade based on their assessment of each patient's degree of disability. Patients, who were blinded to the nurses' assessment, were subsequently instructed to assign themselves an mRS score with the aid of a standard form providing definitions of the mRS scores. Agreement between patients' and nurses' scores was interpreted using a kappa statistic. According to their results, the kappa coefficient for agreement between patient- and nurse-reported mRS scores was 0.58 (95% CI 0.49–0.67).⁴

Using a kappa coefficient to assess agreement of a qualitative variable is not always appropriate and is not reliable in some circumstances. The kappa value is appropriate for nominal variables and also dependent on the number of categories. In such a situation, our suggestion for estimating unbiased results is to apply a weighted or Fleiss kappa.^{1–3} Tables 1 and 2 show that kappa (0.43) and weighted kappa (0.63) have different values in assessing agreement in the above situation. In this instance, the authors should interpret their results with caution.

TABLE 1. Grade assignments by two raters

Rater 2	Rater 1			Sum
	Grade 1	Grade 2	Grade 3	
Grade 1	60	20	1	81
Grade 2	2	12	4	18
Grade 3	3	11	11	25
Sum	65	43	16	124

TABLE 2. Kappa and weighted kappa values for calculating agreement between two raters for more than two categories

Statistic	Estimate	Lower	Upper
Kappa	0.43	0.31	0.55
Weighted kappa	0.63	0.52	0.74

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References

1. Gisev N, Bell JS, Chen TF: Interrater agreement and inter-rater reliability: key concepts, approaches, and applications. *Res Social Adm Pharm* 9:330–338, 2013
2. Naderi M: Letter to the editor on “Is regular knee radiograph reliable enough to assess the knee prosthesis position?” *J Arthroplasty* [epub ahead of print], 2018 (Letter)
3. Naderi M, Sabour S: Methodological issues on reliability of interpretation of neurologic examination findings for the localization of vestibular dysfunction in dogs. *J Am Vet Med Assoc* 252:1460–1462, 2018
4. Rinaldo L, Johnson DM, Vine RL, Rabinstein AA, Lanzino G: Differences between patient- and professional-reported modified Rankin Scale score in patients with unruptured aneurysms. *J Neurosurg* [epub ahead of print August 10, 2018. DOI: 10.3171/2018.3.JNS18247]

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Response

We would like to thank Shahsavari et al. for their thorough review and critique of our paper. We hope to address their concerns regarding the statistical methodology of our work with the following. Shahsavari et al. point out that when assessing inter-rater agreement of a non-binary categorical variable, the use of a non-weighted kappa statistic can result in biased results. Our understanding is that the weighted kappa is most helpful in accounting for the magnitude of difference between individual rater scores. For example, there is clearly more disagreement between mRS scores 0 and 4 than between scores 1 and 2. In our data set, there was only a single instance in which the patient- and nurse-reported mRS score differed by more than one category. While our numerical results may have differed had a weighted kappa been applied, we suspect that these differences would not have changed our relatively conservative interpretation that there is a moderate amount of disagreement between patient- and nurse-reported mRS scores in this patient population. Moreover, we do not think the readers' criticism is relevant to the main finding of our study—specifically that certain patient characteristics were associated with greater patient- than nurse-reported mRS scores. Nevertheless, Shahsavari et al.'s point is well taken, and we will consider their remarks in future works. We sincerely thank them for their interest in our paper.

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Reanalyze BEST TRIP

TO THE EDITOR: Alali et al.¹ report on a clinical decision rule with high sensitivity in predicting high intracranial pressure (HICP) after severe traumatic brain injury (TBI) (Alali AS, Temkin N, Barber J, et al: A clinical decision rule to predict intracranial hypertension in severe traumatic brain injury. *J Neurosurg* [epub ahead of print September 28, 2018. DOI: 10.3171/2018.4.JNS173166]). The proposed predictors divide into three major (CT-based) and four minor (mix of imaging and clinical) criteria. The development cohort is the ICP-monitored group of the BEST TRIP (Benchmark Evidence from South American Trials: Treatment of Intracranial Pressure) trial.² The validation cohort comes from the COBRIT (Citicoline Brain Injury Treatment Trial).⁷ This is an important clinical contribution because the question of who and when to monitor is very much pertinent in the management of patients with TBI. Furthermore, interesting observations can be made by comparing these data to the original reports from BEST TRIP. Note that in the original trial, signs of HICP based on the impression of interpreting physicians were detected in 90% of both groups randomized (Chesnut et al.,² Table 1). However, the data provided in Alali et al. demonstrate that within the ICP group only 65/150 (43%) did, in fact, develop intracranial hypertension. This could be explained by considering that 1) initial treatments (such as surgery) may have aborted further intracranial hypertension, or 2) that the Alali et al. criteria may perform far better in decreasing false-positive estimation of HICP (this though would require prospective validation). An implication of this observation is that the potentially high false-positive rate of HICP prediction in the original trial could have led to unnecessary (or overzealous) application of ICP-lowering treatments in the imaging and clinical examination (ICE) group. The results of the BEST TRIP trial did indeed show that the ICE group received more ICP-lowering interventions for longer periods of time. Although in this trial an excess of treatments did not lead to higher rates of adverse events or differences in long-term outcomes, the conclusion that these interventions can be used indiscriminately, or that these therapies are benign, remains debatable.^{3,4,6}

The authors remind us that the role of ICP monitoring in directing the treatment of established intracranial hypertension was not a focus of the BEST TRIP trial, rather it compared two management protocols for treatment of severe TBI: one involving ICP monitoring and the other involving serial CT imaging and neurological examination. One suggestion based on the Alali et al. work is to revisit the results of BEST TRIP to try and explore the

question of the role of ICP monitoring in established hypertension. The new prediction rule could be applied to the ICE group to identify HICP patients within that cohort. A reanalysis using patient-level data could then be attempted, comparing the HICP cohort of the ICP-monitored group with the predicted-HICP cohort of the ICE group. Such a comparison could provide some elucidation of the question of which is the better approach for the management of established intracranial hypertension, and could serve as hypothesis generator for a new trial comparing groups with established, or reliably predicted, intracranial hypertension (and at different thresholds). If such a re-analysis is undertaken, baseline severity-adjusted end point analysis should also be given consideration.⁵

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References

1. Alali AS, Temkin N, Barber J, Pridgeon J, Chaddock K, Dikmen S, et al: A clinical decision rule to predict intracranial hypertension in severe traumatic brain injury. *J Neurosurg* [epub ahead of print September 28, 2018. DOI: 10.3171/2018.4.JNS173166]
2. Chesnut RM, Temkin N, Carney N, Dikmen S, Rondina C, Videtta W, et al: A trial of intracranial-pressure monitoring in traumatic brain injury. *N Engl J Med* **367**:2471–2481, 2012 (Erratum in *N Engl J Med* **369**:2465, 2013)
3. Contant CF, Valadka AB, Gopinath SP, Hannay HJ, Robertson CS: Adult respiratory distress syndrome: a complication of induced hypertension after severe head injury. *J Neurosurg* **95**:560–568, 2001
4. Cooper DJ, Rosenfeld JV, Murray L, Arabi YM, Davies AR, D'Urso P, et al: Decompressive craniectomy in diffuse traumatic brain injury. *N Engl J Med* **364**:1493–1502, 2011 (Erratum in *N Engl J Med* **365**:2040, 2011)
5. Murray GD, Barer D, Choi S, Fernandes H, Gregson B, Lees KR, et al: Design and analysis of phase III trials with ordered outcome scales: the concept of the sliding dichotomy. *J Neurotrauma* **22**:511–517, 2005
6. Shafi S, Diaz-Arrastia R, Madden C, Gentilello L: Intracranial pressure monitoring in brain-injured patients is associated with worsening of survival. *J Trauma* **64**:335–340, 2008
7. Zafonte RD, Bagiella E, Ansel BM, Novack TA, Friedewald WT, Hesdorffer DC, et al: Effect of citicoline on functional and cognitive status among patients with traumatic brain injury: Citicoline Brain Injury Treatment Trial (COBRIT). *JAMA* **308**:1993–2000, 2012

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Response

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Rete middle cerebral artery anomalies

TO THE EDITOR: We read with interest the article by Cho et al.¹ (Cho KC, Kim JJ, Jang CK, et al: Rete middle cerebral artery anomalies: a unifying name, case series, and literature review. *J Neurosurg* [epub ahead of print August 3, 2018. DOI: 10.3171/2018.2.JNS1832]). In this article the authors report on a series of 13 patients who had a rete-like configuration of the middle cerebral artery (MCA). They state that the rete MCA is a congenital disease of the cerebral vasculature, which, on occasion, can develop acquired abnormalities such as aneurysms, which are a result of hemodynamic stress on the rete. They also state that the rete MCA has a higher prevalence in Asia.

The authors' primary hypothesis regarding the pathogenesis of these lesions is that of a congenital anomaly resulting from a fusion interference of the main trunk of the MCA during embryonic development. During the 5-mm stage of embryonic development, the internal carotid artery divides into cranial and caudal branches. The anterior cerebral artery (ACA) is a continuation of the cranial branch, and the posterior communicating artery is the caudal branch. The MCA is a branch of the ACA and develops from multiple plexiform arterial twigs, which develop into the lateral striate arteries. Through a process of fusion and regression, the MCA trunk develops. The authors hypothesize that the rete MCA is due to a persistence of the fetal arterial network of arterial twigs that immediately precede the development of the MCA trunk.

While this hypothesis is certainly reasonable, it seems more likely that the "rete MCA" is no more than an acquired abnormality involving the development of lenticulostriate collaterals in the setting of steno-occlusive disease or moyamoya affecting the proximal MCA. In the authors' series, all patients were adults, and most had clinical presentations similar to that of moyamoya and other steno-occlusive diseases with intracranial hemorrhage, acute ischemic stroke, transient ischemic attack, and headache. In their review of the literature, all patients with the so-called rete abnormality were adults, and most had presentations similar to that of patients with moyamoya and other steno-occlusive diseases with a majority of patients presenting with hemorrhage and infarction of the affected territory. The authors state that this abnormality is found almost exclusively in Asians, a finding very similar to moyamoya and other idiopathic forms of steno-occlusive disease.

The fact that this abnormality has primarily, if not exclusively, been reported in adult populations recommends against the idea that this is a congenital abnormality. If it were congenital, one would expect to see pediatric cases of such an abnormality.

The authors also state in Table 3 that one means of differentiating rete MCA anomaly from moyamoya and steno-occlusive disease is that rete MCA anomalies do not progress. However, this is somewhat overstated as the length of follow-up in this study is limited. The natural history of these lesions appears to be dismal as 9 of 13 patients suffered hemorrhage or ischemic complications.

Thus, we caution against using the term "rete MCA anomalies" as a unifying term for this entity. Further study is needed to determine if this is simply an angiographic manifestation of moyamoya or other steno-occlusive disease.

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References

1. Cho KC, Kim JJ, Jang CK, Hong CK, Joo JY, Kim YB: Rete middle cerebral artery anomalies: a unifying name, case series, and literature review. *J Neurosurg* [epub ahead of print August 3, 2018. DOI: 10.3171/2018.2.JNS1832]

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Response

We greatly appreciate the interest in our article, as well as the valuable comments from Drs. Brinjikji and Lanzino.

As mentioned in the paper, there is no clear evidence for us to consider this anomaly as congenital. However, there are rational clues implying that rete MCA is a congenital anomaly, including the unique rete morphology, which should be temporarily visible in the developmental process, and the somewhat different clinical features from the representative, acquired MCA pathologies of moyamoya and atherosclerotic steno-occlusive disease.

As the authors pointed out, it is reasonable to think that a case of congenital disease would exist in a pediatric patient; but for some reason, no example of a pediatric rete MCA patient has been found so far. First of all, screening tests (CTA or MRA) are not often performed on pediatric patients. Moreover, since digital subtraction angiography, which is the gold standard for confirmation of this anomaly, is very rarely performed in children, the occurrence of the rete MCA anomaly may appear to be less frequent. Furthermore, even if clinicians recognize a rete-like anomaly in their clinical tests, it may not be considered the newer entity of anomaly, but is more likely to be diagnosed as moyamoya syndrome, which may be the same as in the adult population. The absence of reported pediatric examples seems, at least partly, to be attributable to all the aforementioned reasons, which may be the same reason we could seldom find pediatric cases with congenital MCA anomalies such as accessory or duplicated MCAs. Even if we found a pediatric case, it might not be enough to prove that rete MCA is congenital, as the moyamoya-like acquired phenomenon can easily affect young children. Therefore, no one can refer to rete MCA as a congenital anomaly until an infant with rete MCA is found directly after birth. After all, it seems extremely difficult to prove the suggested hypothesis by finding representa-

tive pediatric case examples. Nonetheless, the existence of subjects in their teens and 20s in reported cases still seems relevant, at least to be differentiated from the atherosclerotic steno-occlusion.

It is true that the current data are too limited to conclude that rete MCA is not progressive. However, uniquely, we could not find any single case in which the patient had a bilateral lesion, transdural collateral contributions, or any signs of involvement other than an affected M_1 segment. Although a progressive trait, like in moyamoya disease, should have produced various examples of concurrent lesions on the contralateral side, ipsilateral ACA, or even the posterior circulation, a total of 60 cases from a pooled analysis in our article seemed uniquely confined to a distinct feature involving “unexceptionally a unilateral M_1 .” We considered this to be quite a solid clue that suggests rete MCA would not be progressive. In fact, patients in our series who had undergone angiographic follow-up did not show any changes to their vasculature (cases 1, 5, 7, 9, 10, 12, and 13; with a mean follow-up of 27 months). Again, in Seo et al.’s series,³ there was no progression at all in four patients who underwent follow-up studies during a mean follow-up of 31 months, even in a 10-year-old girl on the 16-month follow-up angiogram. Although the follow-up period seems relatively short, it can be enough to witness anecdotal progression when compared to moyamoya disease in which approximately 10%–30% of patients may progress to involvement of the contralateral side within a couple of years.^{1,2,4,5}

As we stated above, we strongly believe that rete MCA is not simply a variant of moyamoya or other steno-occlusive disease, but rather develops from a congenital anomalous process. At the same time, we truly understand the authors’ caution against using the term “rete MCA anomalies” as a unifying term. Therefore, we will conduct further study to provide concrete evidence for these issues, with the hope that many researchers will become interested in this matter.

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References

1. Kawano T, Fukui M, Hashimoto N, Yonekawa Y: Follow-up study of patients with “unilateral” moyamoya disease. **Neurol Med Chir (Tokyo)** 34:744–747, 1994
2. Kelly ME, Bell-Stephens TE, Marks MP, Do HM, Steinberg GK: Progression of unilateral moyamoya disease: a clinical series. **Cerebrovasc Dis** 22:109–115, 2006
3. Seo BS, Lee YS, Lee HG, Lee JH, Ryu KY, Kang DG: Clinical and radiological features of patients with aplastic or twig-like middle cerebral arteries. **Neurosurgery** 70:1472–1480, 2012
4. Smith ER, Scott RM: Progression of disease in unilateral moyamoya syndrome. **Neurosurg Focus** 24(2):E17, 2008
5. Zhang Q, Wang R, Liu Y, Zhang Y, Wang S, Cao Y, et al: Clinical features and long-term outcomes of unilateral moyamoya disease. **World Neurosurg** 96:474–482, 2016

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Predictors for radiation toxicity and tumor control

TO THE EDITOR: We read with interest the work of Aiyama and colleagues¹ investigating whether conformity and gradient indices are predictors for radiation toxicity and local tumor control (Aiyama H, Yamamoto M, Kawabe T, et al: Clinical significance of conformity index and gradient index in patients undergoing stereotactic radiosurgery for a single metastatic tumor. *J Neurosurg* 129 [Suppl 1]:103–110, December 2018). For decades, we have known that successful radiation treatments require these qualities, although the degree to which they need to be refined to further improve treatment is unknown. Their conclusion is that lower conformity is related to improved local control and the gradient index (GI) has no effect on toxicity.

This work is actually investigating the clinical significance of not two but three qualities, as the conformity index (CI), while being a single value, combines two very different parameters: target coverage (which might predict local control) and selectivity/spillage outside the target (which might cause complications). Therefore, looking at the overall CI as a predictor of either local control or toxicity is flawed.

Considering the large range of CIs and GIs, it is not surprising that no correlation with toxicity was detected. The lowest CI was 0.08 and the largest GI was 11.4. These values would be associated with treatment of very small metastases, which are safe to treat, even with a poor conformity.² Conversely, large metastases are usually planned with great attention to conformity and gradient, but despite optimal planning, larger lesions are more prone to local failure and toxicity. This is shown in their data, i.e., their cumulative incidences of local progression were significantly lower in patients with CIs < 0.65 than in those with CIs ≥ 0.65. However, 66% of lesions < 5 cm³ in their study had poor CIs (<0.65), but for lesions ≥ 5 cm³, this dropped to just 26%.

In order to mitigate confounders, volumes were divided into two groups: < 5 cm³ vs ≥ 5 cm³. However, this method would not eliminate volume as a confounding factor; volumes in the < 5 cm³ group range from 0.01 cm³ to 5 cm³, so vary by a factor of 500. Sneed et al.,³ in their study investigating 2200 brain metastases, divided this range into four and found an increasing incidence of symptomatic radiation necrosis; < 1%, 1%, 3%, and 10% for target diameters 0.3–0.6 cm, 0.7–1.0 cm, 1.1–1.5 cm, and 1.6–2 cm, respectively. These four ranges all reside within the < 5 cm³ subdivision, demonstrating that further divisions of volume are required to eliminate bias.

Clearly the authors are not suggesting that the principles of conformity and gradient should be abandoned. Taken to the extreme, no one would suggest that a confor-

imity of 0.01 for a 15-cm³ metastasis is acceptable (this is the CI of a whole brain treatment when the tumor volume is 15 cm³ and the brain volume is 1500 cm³). Similarly, a GI of 100 in a perfectly conformal plan of a 15-cm³ lesion, treated to 20 Gy, would yield a mean brain dose > 10 Gy and have potentially catastrophic effects. The question is, when does further refinement of a treatment plan matter? This has yet to be revealed by a clinical study. In the meantime, we have a duty of care to reduce extraneous dose to normal tissue where possible.

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References

1. Aiyama H, Yamamoto M, Kawabe T, Watanabe S, Koiso T, Sato Y, et al: Clinical significance of conformity index and gradient index in patients undergoing stereotactic radiosurgery for a single metastatic tumor. *J Neurosurg* **129** (Suppl 1):103–110, 2018
2. Nakamura JL, Verhey LJ, Smith V, Petti PL, Lambourn KR, Larson DA, et al: Dose conformity of Gamma Knife radiosurgery and risk factors for complications. *Int J Radiat Oncol Biol Phys* **51**:1313–1319, 2001
3. Sneed PK, Mendez J, Vemer-van den Hoek JGM, Seymour ZA, Ma L, Molinaro AM, et al: Adverse radiation effect after stereotactic radiosurgery for brain metastases: incidence, time course, and risk factors. *J Neurosurg* **123**:373–386, 2015

Disclosures

Mr. Paddick reports being a consultant for Elekta.

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Response

We thank Dr. Alexis Dimitriadis and Mr. Ian Paddick for their careful reading and analysis of our article. As they suggested, the CI is coverage multiplied by selectivity. With our treatment plan for brain metastases, target coverage ranges from 0.98 to 1.0, a range generally accepted by the Gamma Knife Radiosurgical Society. Thus, the CI reflects only selectivity. They stated that looking at the overall CI as a predictor of either local control or toxicity is flawed. However, we are uncertain as to why Mr. Paddick proposed CI as a parameter of good dose-planning.^{1,2}

Dr. Dimitriadis and Mr. Paddick quoted an article written by Sneed and her colleagues.³ However, they did not describe the GI based on target diameters of 0.3–0.6 cm, 0.7–1.0 cm, 1.1–1.5 cm, and 1.6–2 cm. Furthermore, the most serious criticism of their article is that, as we discussed in our article, their cohort consisted of considerable numbers of patients who had multiple brain metastases. Although they did not explain the method applied to GI determination in patients with multiple brain metastases, Paddick's GI cannot be correctly calculated in patients with multiple brain metastases. Nevertheless, according to the helpful suggestions made by Dr. Dimitriadis and Mr. Paddick, we investigated, using our own database, the relationship between tumor control/complications and the CI/GI, along with three tumor volume groups, i.e., < 1 cm³, ≥ 1.0 to < 3.0 cm³, and ≥ 3.0 to < 5.0 cm³, as shown in Table 1. We cannot as yet draw meaningful conclusions and must await the results of further studies using different, larger data sets, hopefully in the near future.

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TABLE 1. Analysis of complications and local recurrence after stereotactic radiosurgery

Vol (cm ³)	No. of Pts	Complication			Local Recurrence		
		HR	95% Confidence Interval	p Value	HR	95% Confidence Interval	p Value
<1.0	212						
CI <0.65	195	0.290	0.043–5.686	0.33	0.804	0.149–14.893	0.84
CI ≥0.65	17						
GI <3.1	111	1.263	0.209–9.600	0.80	2.198	0.610–10.207	0.23
GI ≥3.1	101						
≥1.0 to <3.0	146						
CI <0.65	62	2.566	0.018–4.079	0.43	0.300	0.069–0.930	0.03
CI ≥0.65	84						
GI <3.1	79	2.332	0.496–3.395	0.48	0.967	0.345–2.598	0.95
GI ≥3.1	67						
≥3.0 to <5.0	126						
CI <0.65	52	0.549	0.080–2.396	0.44	0.982	0.260–3.143	0.98
CI ≥0.65	74						
GI <3.1	38	1.003	0.146–4.410	0.99	2.419	0.712–7.624	0.15
GI ≥3.1	88						

HR = hazard ratio; pts = patients.

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References

1. Paddick I: A simple scoring ratio to index the conformity of radiosurgical treatment plans. Technical note. **J Neurosurg** **93 (Suppl 3)**:219–222, 2000
2. Paddick I, Lippitz B: A simple dose gradient measurement tool to complement the conformity index. **J Neurosurg** **105 Suppl**:194–201, 2006
3. Sneed PK, Mendez J, Vemer-van den Hoek JGM, Seymour ZA, Ma L, Molinaro AM, et al: Adverse radiation effect after stereotactic radiosurgery for brain metastases: incidence, time course, and risk factors. **J Neurosurg** **123**:373–386, 2015

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