Letters to the Editor

NEUROSURGICAL FORUM

Parkinson's disease and early subthalamotomy

TO THE EDITOR: We thoroughly read the article by Jourdain et al.⁶ (Jourdain VA, Schechtmann G, Di Paolo T: Subthalamotomy in the treatment of Parkinson's disease: clinical aspects and mechanisms of action. *J Neurosurg* 120:140–151, January 2014), who reviewed subthalamotomy as a surgical treatment for Parkinson's disease (PD). The authors suggested a positive symptomatic effect of surgery on the cardinal motor features of PD, although the valid data are still somewhat limited and there is no Class I evidence yet.

Parkinson's disease is a progressive, neurodegenerative, and disabling motor disorder, and the pathology is a consequence of the degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNc). The authors describe research results on subthalamotomy and its possible neuroprotective effect. We have chosen to take a different perspective by stressing the putative role of subthalamic nucleus (STN) lesions in the modification of PD evolution. For many years it has been known that the parkinsonian state is associated with and features enhanced glutamatergic (excitatory) STN over-activity, which, in turn, could lead to increased dopaminergic cell loss in the SNc, and subthalamotomy could interfere with such putative excitotoxicity. Admittedly, experimental evidence has shown some variable outcomes, but the aforementioned authors failed to demonstrate the neuroprotective effect of 6-hydroxydopamine (6-OHDA) in a rat model^{9,10,13–15} or in monkeys treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP).^{5,8,17} Authors of another article reported no cell-sparing effect of the STN lesion in monkeys treated with MPTP after subthalamotomy.⁸ However, that study cannot be taken into consideration, as its aim was not the identification of the neuroprotective effect of an STN lesion but rather to ascertain the anti-parkinsonian impact of unilateral subthalamotomy.³ Indeed, another prospective study in the MPTP-treated monkey model assessed the impact of STN lesions, and deep brain stimulation of the STN maintained the excitotoxicity hypothesis. The study demonstrated that STN alteration offered neuroprotection to dopaminergic cells.¹⁷ More recently, Jourdain et al. observed no changes in tyrosine hydroxylase immunohistochemistry after a unilateral STN lesion.⁵ Thus, research analysis suggests that the main factor regarding the hypothetical neuroprotective effect of an STN lesion is inversely proportional to the striatal depletion.

We suggest that for subthalamotomy to be neuroprotective, as with any other possible therapy,¹² it should be applied very early after diagnosis. Recently, Kordower et al. demonstrated that the loss of tyrosine hydroxylase in the dorsal putamen fell to 35%–75% at 1–3 years and 70%–90% at 5 years after diagnosis.⁷ This indicates that the time around diagnosis is crucial to protect remaining dopaminergic nigrostriatal cells. Indeed, STN over-activity and the associated excessive glutamatergic release are likely to be present very early after nigrostriatal damage has begun.^{11,16} Accordingly, clinical trials in patients with advanced PD are of no value when considering neuroprotection.

The recent introduction of a novel and noninvasive surgical treatment, transcranial magnetic resonance–guided focused ultrasound (MRgFUS), could provide such an opportunity if the lesion of the basal ganglia target can be used as well, as has been done in the case of thalamic ventral intermediate nucleus ablation.² Magnetic resonance–guided focused ultrasound generates an intracranial lesion and provides clinical benefit to patients with disabling tremor if lesion placement and volume are accurate. Initial reports suggest that the procedure is safe enough to proceed with more comprehensive clinical trials. The possibility of practicing targeting with real-time clinical assessment and MRI monitoring opens a new window to future surgical treatments for movement disorders.

When considering a lesion of the STN, the fear of inducing a hemichorea-hemiballism is indeed a concern. We have argued before that the parkinsonian state, by virtue of the changes occurring in the basal ganglia, increases the threshold for hemiballism after STN lesioning.^{3,4} Indeed, the incidence of hemichorea-hemiballism is about 15% in our experience¹ and persists in 9% in whom the dyskinesia is considered severe, and it is not yet known if the volume and location of the lesion or the patient phenotype makes some patients particularly prone to this complication. The clear advantage of focused ultrasound therapy is that the lesion can be formed slowly and progressively, allowing adjustment of its size and permitting physiological compensatory mechanisms to take place. In conclusion, there may yet be another revival of the oldest approach for functional neurosurgery of movement disorders with a newer technique. Proving this could impact PD's progressive evolution.

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DISCLOSURE

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Response

First, we thank Guridi and Obeso for their insightful comments. The purpose of our article was to uncover the clinical aspects, complications, as well as the biochemical and cellular effects of subthalamic lesions. Guridi and Obeso present their perspectives on the possible neuroprotective effect of this lesion-based surgery for PD, which they say are in opposition to those in our review article. But we do not disagree with these authors. Subthalamotomy may indeed be neuroprotective, but several factors must be considered.

Glutamate plays a major role in the motor pathways of the basal ganglia. The STN is the only source of glutamate intrinsic to the basal ganglia. Although there is no direct evidence of a role for glutamatergic excitotoxicity in PD, several lines of evidence do suggest a toxic effect.^{2,7,12} The progressive loss of dopaminergic cells in PD causes the STN to disinhibit. In fact, there is much evidence of increased activity in the subthalamic neurons in both PD patients and animal models of PD.^{3,26} Such an increase in STN activity in PD raises the possibility of a contribution to degeneration.

The connection between the STN and the SNc is well established.^{5,17} This subthalamonigral glutamate-enriched pathway may promote sustained excitation of dopaminergic cells. In fact, lesioning of the STN causes a decrease of striatal dopamine in otherwise normal monkeys.²⁰ In the presymptomatic phase of PD, STN-increased activity is believed to serve as a compensatory mechanism for the loss of dopamine.⁴ However, it may exert an opposite effect in the long term. In fact, because of a high expression of glutamate receptors,¹⁸ dopaminergic neurons may become highly sensitive to increased glutamatergic stimulation, and oxidative stress¹⁰ and its neuronal degeneration may accelerate.

Subthalamotomy is one of the options currently offered to patients with disabling levodopa-induced dyskinesia,¹ which comes late in the disease, after several years of treatment.⁹ As mentioned in our review, neuroprotection cannot be considered in this clinical setting. As pointed out by Guridi and Obeso, as well as other authors,¹⁶ neuroprotection in advanced PD is too late. Therefore, the key factor is an early but accurate diagnosis. Spatial covariance analysis of the resting state metabolic network is among one of the best tools for accurate differential diagnosis.²⁴ On the other hand, an early diagnosis is much harder to achieve. Although transcranial MRgFUS may be a novel, noninvasive surgical treatment for PD, the mentality of neurosurgeons should move from a reactive to a proactive state in favor of neuroprotective surgery. In fact, there is a trend toward such a change.¹⁹ Still, we agree that neuroprotection could be achievable within a short time frame after a very early diagnosis. A question remains: Would a subthalamotomy very early after diagnosis be enough to slow down the degeneration? Wallace and colleagues demonstrated a neuroprotective effect of subthalamotomy when performed before exposure to the neurotoxin MPTP.²⁵ In that study, the monkeys were ex-

posed to enough MPTP for an approximate degeneration of 50% of dopaminergic cells, which would replicate the status of an early diagnosis. There is generally no further degeneration of the midbrain cells after they are exposed to the neurotoxin MPTP, which makes it hard to draw conclusions for slowing down the neuronal loss. Clinical trials on the possible neuroprotective effects of subthalamotomy are therefore warranted.

One may also keep in mind that the centromedian-parafascicular thalamic nuclei (CM/Pf) and the pedunculo-pontine nucleus (PPN) are also important sources of glutamate to the basal ganglia. Though it degenerates in PD,⁸ the CM/Pf has no relation with dopamine neurons,^{21,23} and its lesioning has no efficacy in treating PD.¹³ On the other hand, besides the STN, the PPN may be another target for neuroprotection. The PPN directly projects to the SNc in monkeys¹⁵ and bears both cholinergic and glutamatergic projections.¹⁴ Unilateral lesioning of the PPN by stereotactic injection of kainic acid, prior to systemic exposure to MPTP, protected dopaminergic cells from degeneration and reduced parkinsonian symptoms in monkeys.²² Approximately 50% of the cholinergic neurons of the PPN degenerate in moderate to advanced PD.^{6,11,27} The extent of the noncholinergic (and therefore glutamatergic) neuronal loss remains to be determined. Hence, the glutamatergic neurons of the PPN, in addition to the STN, may be an interesting target for neuroprotection.

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Complications in neurosurgery: the need for a common language

TO THE EDITOR: We really enjoyed reading the paper by the Rolston et al.² concerning the critical issue of complications in neurosurgical patients (Rolston JD, Han SJ, Lau CY, et al: Frequency and predictors of complications in neurological surgery: national trends from 2006 to 2011. *J Neurosurg* 120:736–745, March 2014). Health care data analyses are being more and more considered by doctors, researchers, and administrators with the aims of improving quality of care, developing an evidence-based approach to medicine, and reducing costs; the authors should be praised for their valuable contribution to this matter. We believe in fact that these useful data analyses could guide research choices in medicine.

Since 2011 all neurosurgical complications have been registered in our neurosurgery unit at the Fondazione IRCCS Istituto Neurologico Carlo Besta, in a dedicated database built on the groundwork of the complication classification proposed by Landriel Ibañez and colleagues.¹ We would like to compare our data with US data; however the lack of a common language, in terms of complication definition and classification, makes this difficult and possibly misleading. In a world in which economic pressure on the health system is increasing and politicians are committed in controlling costs, this absence of a common language is dangerous for the neurosurgical community and, most importantly, for the patients.

The risk, indeed, is that centers are evaluated and weighted more on costs than on the quality and results of treatments. The parameters used to assess and measure neurosurgical quality seem to have been developed while ignoring the meaning of the numbers and data available. How does the Besta Institute's complication rate compare with the US complication rate? This apparently easy question has no answer if we do not agree on a common definition of the term "complication." The definitions of the terms used by Rolston et al.² as criteria to include cases in the database are not given, but they are essential for a productive comparison. In the *Discussion* section, for example, a late rebleeding after partial removal of an arteriovenous malformation seems to be considered a complication by the authors, whereas in our opinion it should be included in the list of patients who received an "incomplete cure." Since we are dealing with brain and spinal cord, unfortunately the search for a compromise between the extent of resection and the preservation of a good quality of life (QoL) makes this category not numerically negligible. This is why in our view "incomplete cure" should be seen as a category worth considering separately in neurosurgical patients.

How neurological deficits due to the manipulation of eloquent nervous structures were considered and classified is not mentioned either. How were neurological deficits that can follow neurosurgery and that so much impact patients' and caregivers' QoL considered? Was facial nerve damage following removal of a large acoustic neuroma considered a complication? What about hemiplegia or aphasia that can follow the removal of a tumor in an eloquent area? Answers to questions like these can radically

change the rate of complications of a specific neurosurgical series (and thus the data and the costs related to the treatment of these occurrences). Based on these observations it is clear that the definitions of the main terms that are used to describe the outcome of neurological surgery should be agreed upon and common in the scientific international community.

In this view we should consider 3 main categories of undesired outcomes that can result from neurosurgery: 1) complications; 2) sequelae; and 3) incomplete cure. It is necessary to define each of these categories so that a clear taxonomy can be built and shared in the neurosurgical community.

If we use the term "complication" as synonymous with "undesired outcome," probably we should accept the fact that in the American College of Surgeons' National Surgical Quality Improvement Program (ACS NSQIP) database all of the neurological deficits that are common in neurosurgery and that derive from posttraumatic surgical injury to eloquent nervous structures are neglected. Numbers can dramatically change following the decision to include or exclude these cases: in data of centers such as the Besta Institute (a national high-volume dedicated neurosurgical center where only elective surgery is performed) the complication rate can be as low as 2% if we exclude sequelae and as high as 10% if we include also transient neurological deficits (sequelae) that are already fully resolved at discharge. Since these numbers count for administrators on one side and for patients on the other side, discrepancies due to lack of a conventional common definition of the word "complication" (as well as of its meaning) are unacceptable.

The issue of "incomplete cure" is also delicate. A paradigmatic example of this complexity is represented by the case of a left fronto-opercular low-grade glioma that is only biopsied in a low-volume center to avoid sequelae (complications?) or that undergoes gross-total removal with transient postoperative language disturbances in a specialized dedicated center. What about reimbursement? Should it be equal for both centers? Should it be higher for the low-volume center that avoids the transient deficit or for the high-volume dedicated center that had to treat the sequela? Administrators cannot answer these questions without the help of the neurosurgical community. There are cases in which a neurological posttraumatic deficit is somehow unavoidable (e.g., surgery of the spinal cord, in the brainstem, deep brain areas, skull base, motor and language areas). In these cases, only if the procedure is excellently performed will the deficit be slight and will the patient recover quickly; but high-volume centers that treat the most challenging lesions are exposed to the paradox of having the highest complication rate overall. These deficits should be named, in our opinion, "sequelae" and not "complications."

Indicators of performance that take into account the quality of the result for the patients are needed by the neurosurgical community. Equally, it is urgent that we provide administrators with these indicators before the different interpretation of the same words brings unnecessary risks.

In the last few years the number of papers focusing on complications and QoL in neurosurgery fortunately has increased, producing a growing interest of the neurosurgi-

cal community in this topic. This paper by Rolston et al.² will remain as a landmark of this trend, and our hope is that starting from what we know and identifying what is still lacking, we will be able to promote and stimulate a fruitful debate to reach an agreement on the terminology and definitions to be used to describe adverse outcomes in neurosurgery.

After having reached this compromise we should concur on a common classification of complications, in agreement with international scientific societies, and involving in this exercise also the World Federation of Neurosurgical Societies and the WHO. This classification should immediately allow for the identifications of those weak areas that require attention to increase patients' safety.

Complications should be better evaluated if they have to be classified into etiological categories rather than into the kind of treatment required. Administrators should receive from our community the tools for a correct outcome evaluation. These instruments are necessary to drive economic resources toward efficacy and efficiency. A great effort from the neurosurgical community is required to increase a culture able to turn this period of economic uncertainty into an opportunity to improve the quality of neurosurgical treatments on a large scale.

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DISCLOSURE

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Response

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Quality of life of patients affected by unruptured brain AVMs

TO THE EDITOR: We read with great interest the study by Bervini et al.¹ (Bervini D, Morgan MK, Ritson EA, et al: Surgery for unruptured arteriovenous malfor-

mations of the brain is better than conservative management for selected cases: a prospective cohort study. *J Neurosurg* 121:878–890, October 2014). In their study the authors showed surgical treatment of Spetzler-Ponce Class A AVMs is superior to no treatment. We think this is a key paper for all surgeons involved in this fascinating field. Indeed, it can definitively clarify the role of surgery in the management of unruptured AVMs, “providing robust support for recommending treatment.”³ In addition, both the large size of the patient group and the rigorous method of data analysis made the study an objective reply to the results of ARUBA (A Randomized Trial of Unruptured Brain Arteriovenous Malformations).⁸ After this response, we believe that the field is ready for new questions. Unruptured brain AVMs are frequently symptomatic and sometimes disabling. Indeed, the quality of life (QOL) of a patient with an unruptured AVM can be limited by different factors, such as seizures, the need for antiepileptic medication, and neurological defects, which can have a substantial effect on daily activities, life plans, work ability, social life, and other aspects of the patient's life. The risk of bleeding, and the risks associated with AVMs in general, can be perceived in different ways by patients with these lesions, sometimes influencing the treatment decision. Bervini et al. reported that seizures and neurological deficits were present in 47.9% and 12.1% of patients with Spetzler-Ponce Class A, and in 57.9% and 17.8% of those with Spetzler-Ponce Class B unruptured AVMs, respectively. We are all aware that surgery can play a crucial role in treating these conditions and thus improving quality of life. For example, we know from literature that surgery can effectively eliminate seizures in AVM patients.^{4,5} QOL assessment is a widely used measurement of outcome of clinical trials and is increasingly recognized as a major end point for Phase III randomized controlled trials.² The attention to QOL is a well established in neurooncological patient treatment,⁷ and it represents an emerging issue for patients undergoing cerebrovascular surgery.⁹ For example, some authors have shown that the preoperative QOL of patients with unruptured aneurysm is lower than for the normal population, and that surgery improves the QOL of such patients.^{6,10,11} We think that the next step, now, is to focus our attention on how we can improve the QOL of patients with unruptured brain AVMs. This new perspective might open a new and interesting scenario for treatment in general, and surgery, in particular, for these patients. In our department we recently started QOL assessment of AVM patients undergoing surgery, and we frequently registered both a lower preoperative score compared to normal population scores and an improvement of QOL after surgery. We wanted to share our observations with the neurosurgical community involved in this fascinating field and suggest some questions that have arisen as a result of our reading the paper by Bervini et al. Could QOL assessment be a new, modern, more appropriate way to compare different treatment options of patients affected by brain AVMs? Could surgery improve QOL of patients affected by Spetzler-Ponce Class B AVMs more than no treatment? Should we make the QOL of AVM patients central in our decision-making process? We thank Professor Morgan and coworkers for their remarkable work providing us data

showing that surgery, in expert hands, is able not only to cure patients but probably also to improve the quality of their lives. We keep investigating.

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DISCLOSURE

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Response

We believe that Drs. Della Puppa, Rustemi, and Scienza have made an excellent point regarding the importance of studying brain AVM treatment from the point of view of the patient with regard to QOL. Developing instruments to measure this (e.g., the SF-36 [36-Item Short-Form Health Survey]) is important and commendable. There is no doubt that with time and progress in surgery, the outcome measures employed have evolved to increase our understanding of outcomes from “good,” “bad,” and “dead” to a greater outcome range used today. The future will see a shift to more sophisticated outcome measure scores. Hopefully, this will be matched by innovations and improvement in surgical care. We do measure SF-36 and neuropsychological outcomes at our institutions for our more recent patients to improve our understanding of the impact of management decisions (e.g., neuropsychological outcomes¹). We are fortunate to have dedicated personnel that can be devoted to this task.

However, moving to more personalized and complex evaluation tools has significant challenges. The more we move away from the binary outcome system of alive or dead, which can be easily assessed and validated by many,

FIG. 1. Kaplan-Meier analysis of the first seizure following surgery for supratentorial brain AVM. SPC = Spetzler-Ponce Class.

TABLE 1. Number at risk for Fig. 1

Description	Year																
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
No. at risk: supratentorial SPC A	317	201	129	84	65	48	35	29	23	19	18	13	10	6	5	3	1
No. at risk: supratentorial SPC B & C, no preop seizures	142	85	54	37	28	25	21	15	9	7	3	2	2	1	1	1	1
No. at risk: supratentorial SPC B & C, preop seizure	102	55	36	24	19	15	11	9	7	7	5	4	4	2	0	0	0
Total	561	341	219	145	112	88	67	53	39	33	26	19	16	9	6	4	2

SPC = Spetzler-Ponce Class.

the greater the challenges for accuracy and compliance. Patient-centered QOL instruments (e.g., SF-36) can be very difficult tools to apply with 100% compliance because of the greater commitment to time and effort required of both the patient and the treating team, the uncertainty as to the way individuals may assess their QOL from time to time, and translating the interpretation of these QOL outcomes to the informed consent process for future patients. As an example, on evaluating neuropsychological outcomes with dedicated staff for this purpose, we were successful in recruiting fewer than 60% of eligible patients.¹

In addition to QOL, there is also the interpretation of what an individual is willing to trade. For example, parents may consider surgery worthwhile if it will result in a slight hemiparesis or homonymous hemianopia of their child presenting with a hemorrhage from a Spetzler-Ponce Class C brain AVM in order to reduce the chance of their child's dying before they do, whereas many adults will not accept this outcome. Furthermore, the perceived QOL may not be fixed over time. Someone believing that they have a good QOL at one point in time may not have a fixed view of it at another. Therefore, judging QOL is a difficult measure to make and interpret and results in an extraordinarily difficult measure to apply to guide future management.

It would be a mistake to assume that the simple-to-apply modified Rankin Scale (mRS) reflects fully patients' perception of their QOL. However, we believe that the mRS is useful as a measure that allows rough benchmarking between units for each Spetzler-Ponce class or Spetzler-Martin grade. Having said this, we did find correlation between mRS outcome scores and more detailed outcome evaluation, reassuring us that the mRS remains useful.¹

Drs. Della Puppa, Rustemi, and Scienza point out the importance of seizure management with regard to the impact upon QOL. Our preliminary results for Kaplan-Meier analysis of first seizure following surgery for supratentorial brain AVMs (both ruptured and unruptured) is given in Fig. 1, with the number at risk reported in Table 1. These results suggest that in our hands, the potential to "effectively cure seizures" (as commented upon by Drs. Della Puppa, Rustemi, and Scienza) is uncertain and less dramatic than previously reported.

We welcome Drs. Della Puppa, Rustemi, and Scienza's plans to encourage the application of more sophisticated outcome measures. The more lenses that we can apply, the more that we will understand. We are sure that the experience of surgery changes patients, and measuring these changes is important. We also need to understand how to

interpret and apply the outcomes measured and translate these for intended patients.

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Knosp Grades 2–3 nonfunctioning pituitary adenomas

TO THE EDITOR: We read with pleasure the article by Dallapiazza et al.¹ that reports on a retrospective analysis of a concurrent series of 99 patients with nonfunctioning pituitary adenomas treated by a well-experienced and renowned surgical group (Dallapiazza R, Bond AE, Grober Y, et al: Retrospective analysis of a concurrent series of microscopic versus endoscopic transsphenoidal surgeries for Knosp Grades 0–2 nonfunctioning pituitary macroadenomas at a single institution. *J Neurosurg* 121:511–517, September 2014). This study evaluated patients with Knosp Grades 0–2 tumors to compare the results of two different surgical techniques. Fifty-six patients underwent a fully endoscopic transsphenoidal resection, whereas 43 underwent a transsphenoidal microscopic resection. No statistical differences were noticed between the two groups in terms of extent of resection and endocrinological complications. For patients with Knosp Grades 0 and 1 macroadenomas, results similar to those previously reported by us² were demonstrated. Therefore, both studies confirm the assumption that for an experienced neurosurgeon, no differences exist in terms of the extent of resection for clearly noninvasive pituitary adenoma. For Knosp Grade 2 nonfunctioning pituitary adenoma, however, the situa-

tion is more complex. We agree with Dallapiazza et al. that Knosp Grade 2 adenomas are not invasive and that there are doubts regarding true invasion of the cavernous sinus in many tumors classified as Knosp Grade 3 adenomas. According to our experience,² gross-total resection (GTR) was achieved in 88% and 67% of endoscopically treated Knosp Grades 2 and 3 cases, respectively, compared with 47.8% and 16.7% of cases treated with microscopic surgery. Note that we did not perform an endoscopic transcavernous approach in these tumors and that the good rate of GTR in this patient subgroup was entirely attributable to the extensive opening of the sellar floor, a clear advantage of the endoscopic technique.

The study conducted by Dallapiazza et al. showed no statistically significant correlation between the endoscopic and microsurgical techniques for each subgroup of Knosp grade tumor in relation to the probability of achieving a GTR. This result could be partly due to the fact that their study was restricted to tumors of Knosp Grades 0–2. In our series, however, we compared results between the surgical techniques in all subgroups of Knosp grading. The endoscopic technique was clearly superior to microsurgery in the Knosp Grades 2–3 subgroups whereby the laterosellar extension determined the quality of resection and thus the cure rate for nonfunctioning adenomas. The endoscopic procedure allows a panoramic view from one internal carotid artery to the contralateral one, and thus permitting a more extensive resection than that allowed by the purely microscopic approach (which is restricted primarily to the midline for direct vision). Furthermore, an improved laterosellar view is obtained with the use of 30° and 45° endoscopes.

One major difference between the Dallapiazza and colleagues study and ours is the fact that their series was concurrent while ours was consecutive and that their study was conducted in a short period of time with results originating from the same surgeon. Although surgeon experience could influence the result, the study period for the microsurgical technique in our series did not include the learning curve for the senior surgeon, whereas the learning curve for the endoscopic technique was included. This bias may only negatively impact the endoscopic technique. Our study also showed superior results for the upper part of the adenoma, and the height of the tumor was a factor of paramount importance for the tumor remnant. In our experience, the endoscopic approach allowed better access to the suprasellar or even subfrontal extensions.

Dallapiazza et al. do not comment on the improvement of preoperative endocrine deficits following surgery. Our study showed significant improvement in postoperative endocrine deficits following the endoscopic technique (56%) compared with the improvements attained following microsurgery (25%). Finally, we found that the incidence of CSF leaks was higher with the endoscopic technique but that this was subsequently overcome by the surgeon's increased experience with this technique.

Actually, these two papers feature retrospective studies with small sample sizes that may affect statistical results in both directions and prevent any definitive conclusions. However, it seems reasonable to assume that for small tumors without lateral extensions, no difference has to be ex-

pected. If a difference between the two techniques exists, it should probably be expected for a high-grade tumor volume in which endoscopy has a clear advantage in increasing surgical access through extended approaches. The contrasting results of these two studies underline the need for larger, well-designed multicenter studies to decide on the value of either operative technique in determining the quality of resection in Knosp Grades 2–3 groups.

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DISCLOSURE

The authors report no conflict of interest.

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Response

We thank Dr. Messerer and colleagues for their comments on our study in which we compare the surgical outcomes of microscopic and endoscopic transsphenoidal surgery for Knosp Grades 0–2 nonfunctioning pituitary macroadenomas. Messerer et al. previously compared microscopic and endoscopic surgery for nonfunctioning pituitary macroadenomas in consecutive patients.³ The results of our study and those of Messerer et al. are similar for Knosp Grades 0 and 1 adenomas. In contrast to our results, however, they found significant improvement in the rate of GTR and endocrinological recovery in the group that underwent endoscopic surgery rather than microscopic surgery for Knosp Grade 2 (and 3) adenomas. From their results, they concluded that endoscopic surgery is superior for laterally extending adenomas.

The aim of our study was to compare the results of microscopic and endoscopic surgery for a group of patients without significant lateral extension or cavernous sinus invasion. We were interested to know if there were differences in outcomes for the adenomas for which GTR was expected. Although the original report by Knosp et al. described a high rate of cavernous sinus invasion for adenomas that crossed the midline of the intracavernous segment of the internal carotid artery (ICA) but did not cross the lateral tangential line of the ICA (Knosp Grade 2),² we found that a significant portion of Knosp Grade 2 growth hormone (GH)–secreting adenomas do not in-

vade the cavernous sinus and are surgically curable.^{1,6} For Knosp Grade 3 GH-secreting adenomas, there is a much lower remission rate using either method because of lateral cavernous sinus invasion.^{1,6} We believe that it is inappropriate to combine Knosp Grades 2 and 3 tumors together. Instead, Knosp Grade 3 tumors are more properly grouped with Knosp Grade 4 tumors. In designing our study under discussion, we included only patients with Knosp Grades 0–2 adenomas and excluded those with adenomas that had a high likelihood of cavernous sinus invasion. We concluded that the microscopic and endoscopic techniques provide similar outcomes for patients who do not have cavernous sinus invasion beyond the medial cavernous sinus. For patients in whom GTR is expected, the endoscope and microscope perform equally well.

In our experience, the sublabial, microscopic transsphenoidal approach provides a midline surgical corridor that can expose the sella from cavernous sinus to cavernous sinus, and the sellar floor to sellar tuberculum for extended approaches. This allows full surgical exploration of the sella, medial cavernous sinus walls, and suprasellar space. In our study, there was a 76% rate of GTR of Knosp Grade 2 adenomas using the microscopic approach, as compared with 47.8% in the study by Messerer et al.³ Notably, in Messerer and colleagues' study, a tumor remnant after microscopic surgery was found in the suprasellar space in nearly 25% (10 of 41) of cases and within the sella in more than 25% (11 of 41) of cases. Tumor remnants in the cavernous sinus accounted for the remaining approximately 50% (20 of 41) of cases. Although we did not report the location of adenoma remnants in our study, most residual adenomas, whether after the microscopic or endoscopic method, were located laterally in the region of the cavernous sinus and not within the sella or suprasellar space.

For invasive Knosp Grade 3 adenomas in the lateral aspect of the cavernous sinus, the expanded view afforded by the endoscope can lead to a greater degree of adenoma resection under direct visualization. However, with tumor lying in the medial portion of the cavernous sinus, the microscope can be used to successfully remove invading tumor, as can the endoscope, and either method can be used when it is appropriate. On the other hand, when adenomas invade the cavernous sinus beyond the medial wall, it is highly unlikely that complete resection can be achieved because of microscopic residual tumor.⁴ Notably, one must consider the surgical goals when assessing the quality of resection. In our opinion, for nonfunctioning pituitary macroadenomas, the goals of surgery are to decompress the optic apparatus, preserve pituitary function, remove as much tumor as can be safely removed, and avoid neurological or surgical complications. In the case of noninvasive adenomas, these goals can be achieved while performing a complete resection. For noninvasive tumors, however, a "quality resection" does not necessitate aggressively debulking the lateral portion of adenomas invading the cavernous sinus.

In their study, Messerer et al.³ stated that improved visualization with the endoscopic approach allows for identification of the compressed anterior pituitary gland that is "never seen during microscopic surgery," leading to better postoperative pituitary function. During microscopic

and endoscopic pituitary surgery, by using the histological capsule of the tumor as a surgical capsule, we routinely identify and preserve the compressed anterior pituitary gland during dissection. There was a very low rate of new endocrinological deficiency using both methods in our study, which is comparable to the results reported by Messerer et al.

Given the results of our study, we assert that for non-invasive nonfunctioning pituitary macroadenomas for which complete resection is expected, there is no difference in the rate of GTR, postoperative endocrine outcomes, or surgical complications using the microscopic or endoscopic method for resection. Since we consider most Knosp Grade 3 adenomas to be invasive and more appropriately grouped with Knosp Grade 4 adenomas, they were excluded from our study, and thus we cannot compare the results for Knosp Grade 3 adenomas with those reported by Messerer et al.³ Comparing the extent of resection for Knosp Grades 3 and 4 adenomas would be a valuable future study. However, it is noteworthy that the difference in the results between the two studies of Knosp Grades 0–2 tumors was with the use of the microscope in Grade 2 tumors (47.8% GTR in their study vs 76% in ours), a difference that may have been produced by our routine focus on the margin of the pseudocapsule during tumor resection.⁵

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