We would like to congratulate Marston et al. for their very nice contribution concerning the influence of the growth pattern of sporadic vestibular schwannoma (VS) before stereotactic radiosurgery (SRS) on the growth pattern after SRS. The Mayo Clinic group under the leadership of Bruce Pollock have published 2 of the 5 comparative studies demonstrating the superiority of Gamma Knife radiosurgery (GKS) over microsurgical resection in small- to medium-sized VSs. In particular, these 5 studies have demonstrated a much lower risk of motor facial palsy and functional hearing loss with radiosurgery. The authors propose systematic “wait and scan” management in the setting of sporadic minimally symptomatic VSs that are < 2 cm in diameter.

In the present prospective study, the authors’ intention was to include all patients observed for a period of at least 6 months (with a > 1-mm/year increase in tumor size). However, from a cohort of 432 patients treated between 2004 and 2014, the authors were able to enroll only 68 patients (15.7%). Among 59 extracanalicular VSs, 85% (50) were reduced or stable and 15% (9) enlarged by > 2 mm, including 5 treatment failures (8.5%) requiring a new intervention (3 GKS and 2 resections). As reported some years ago by this group, their rate of failure during this period of time was higher than what might be expected from other expert centers, and higher than that previously reported by the same team. The annual growth of the stable and decreased tumors was significantly lower than that of the subgroup displaying increase (2 mm/year vs. 3.26 mm/year). Interestingly, the preoperative growth was not different between those VSs reducing in size versus those remaining stable. The authors describe a threshold of annual growth of 2.5 mm; 97% of those with lower annual growth were afterward in the stable or decreasing group, and only 69% were in the group with a higher annual growth. It is of the utmost importance to note that in this study some patients were followed up for as little as 14 months, and among the patients in whom the selected treatment failed, some underwent salvage therapy as early as 2 years after radiosurgery!

In 2002 we reported that a significant percentage of our patients demonstrated transient tumor growth (see Fig. 1) without any predictive value for the long-term outcome in terms of tumor control. However, in the subgroup of patients who presented with a marked increase in tumor volume between time of diagnosis and intervention (35%), the postoperative growth was more marked. But in the subgroup of patients in whom an increase in volume of > 30% of the extracanalicular portion was seen between diagnosis and treatment, we found an average tumor decrease of 40% at 4 years.

As pointed out by the Mayo team years ago, various patterns of response to radiosurgery may occur. Thus, this variability and the observation of transient tumor increase...
as part of the normal response of the VS to radiosurgery may explain some of the somewhat surprising findings of Marston et al. Consequently, and as emphasized by the authors, there is no clear consensus on the criteria for the diagnosis of tumor control and/or treatment failure. For years it has been a common thought that, 3 years after radiosurgery, a tumor that was bigger than at the time of radiosurgery represented a treatment failure. Individual patient experiences have shown us that this was a misconception. On several occasions we proposed resection at 3 years after GKS to patients presenting with a major increase of their tumors, who were then lost to follow-up but who came back more than 10 years later, having not undergone operation, with tumors demonstrating long-term stabilization or shrinkage (Fig. 2).

In 2008 Delsanti et al. published a study of morphological changes in a cohort of 332 patients with VSs treated by GKS between 1992 and 2004 in Marseille. With a mean follow-up of 4.6 years, we observed transient loss of contrast enhancement in 213 patients (68%), a significant increase at 6 months in 178 patients (54%), and a volume at 3 years that was still higher than at the day of radiosurgery but that remained stable in 74 patients (22.3%). We have learned by following these patients for longer periods that they did not in fact experience radiosurgery failures. In Fig. 3 the second group (triangles) displays a > 50% in-
crease at 6 months, 1 year, 2 years, and 3 years, but is starting to show size reduction only between 3 and 5 years. By the end (at 10 years), the efficacy of radiosurgery has been demonstrated—with close to a 50% reduction in tumor size compared with the size at the time of radiosurgery.

If we compare these to patients considered to have experienced radiosurgery failures (16 patients), the mean initial tumor growth at 6 months is almost the same (53% for treatment failure vs 50% for increased size without failure), but the tumors in which treatment failed went on growing more rapidly (at 1 year, mean growth 75% vs 52%; at 2 years, mean growth 207% vs 58%). Thus, in our experience the diagnosis of failure requires a longer follow-up to distinguish between treatment failures and so-called late responders. In light of our experience, to define transient tumor swelling as a phenomenon occurring only at the first or second MRI (obtained at 6–12 months), followed by decrease or stabilization at 2 years, is too limiting. In our experience, transient growth induced by radiosurgery, followed by stabilization or decrease, can occur as late as 3–4 years after radiosurgery.

In terms of hearing preservation, like the authors, we are disappointed by the very poor follow-up they were able to secure in these patients: only 11 of 33 patients with functional hearing at the time of radiosurgery underwent pre- and post-GKS audiometry! The rate of functional hearing preservation is especially poor here (36.4%) compared with results achieved by other expert centers. This may be biased by the small size of the sample. It may also be the price to pay for the systematic attitude that proposes that wait and scan may be beneficial in cases of long-term stability of the tumor. However, large meta-analyses of the literature have shown that given patient life expectancy, it is likely that the vast majority of these tumors will grow. Even worse, the consequence of this attitude may also be to prevent the patient from benefiting from a window of opportunity for functional hearing preservation. Based on these data from the literature and our experience, we suspect that with earlier radiosurgery and longer follow-up before declaring failure, the authors may reach significantly different conclusions.

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Disclosures

Dr. Régis is a consultant for Medtronic and Elekta.

Response

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On behalf of my coauthors, we are very grateful to Régis et al., and the editorial board of Journal of Neurosurgery, for the opportunity to respond to the many intriguing comments in the Marseille group’s editorial, some of which directly pertain to our manuscript appearing in this issue. As noted, Pollock et al. published the first prospective cohort study in 2006, now a decade ago, comparing SRS and microsurgery in patients with VS. A very similar prospective nonrandomized study comparing SRS and microsurgery reported in 2009, by the group in Bergen, Norway,
reached identical conclusions: SRS resulted in better short-term clinical outcomes regarding hearing preservation and facial nerve function.\textsuperscript{13} The median follow-up was 42 and 24 months, respectively, in these 2 important analyses.

What was missing from these studies, of course, was an “observation” arm. Subsequently, Breivik et al., from Bergen, performed a prospective, nonrandomized study comparing SRS (n = 113) with observation (n = 124).\textsuperscript{1} After a mean follow-up period of 55 months, there was no significant difference in hearing outcomes between the 2 groups. In other words, proactive treatment with radiosurgery did not result in improved hearing outcomes over the natural history in this study. Stereotactic radiosurgery resulted in significantly fewer patients requiring additional treatment compared with patients who had no initial treatment (observation). Moreover, the collaboration between Mayo Clinic and our colleagues in Bergen has also recently demonstrated very little impact of treatment modality on long-term quality of life in patients with VS.\textsuperscript{3,4}

That is, we aren’t necessarily making symptoms better in patients with VS by treating their tumor. Frankly, since the landmark work from the group in Copenhagen, Denmark, was first reported at the quadrennial Fourth International Conference on Vestibular Schwannoma and Other CPA Lesions in Cambridge, England, in July 2003, and their subsequent very thoughtful publications, we have become convinced—as have other authors—that we are probably overtreating patients with VS in the US.\textsuperscript{5,12,19} Thus, as Régis et al. note, we have adopted a “wait and scan,” approach to most patients with small VSs at the Mayo Clinic. One of the most often heard criticisms of SRS for VS that we encounter is that this treatment modality is simply taking credit for a tumor with a very benign natural history. Approximately 70% of observed tumors show no growth during the first 3–4 years of follow-up, which is the average follow-up period of most radiosurgery series reporting > 90% tumor control.\textsuperscript{19}

In our manuscript, “Pretreatment growth rate as a predictor of tumor control following Gamma Knife radiosurgery for sporadic vestibular schwannoma,” we report on 68 patients who had documented growth prior to undergoing SRS at our institution. The primary finding of our study is that patients with tumors that were growing at a rate $\geq$ 2.5 mm/year were significantly less likely to go on to have radiographic tumor control (tumor control in 69% of cases) compared with the cohort in which lesions were growing < 2.5 mm/year (tumor control in 97% of cases). This was not a prospective study, unfortunately; therefore we were constrained to only include patients for whom we had all of their imaging studies since diagnosis, then those demonstrating tumor growth, through treatment and at least 1 year of post-SRS follow-up imaging. This resulted in a total of 473 MRI scans that were reviewed for these 68 patients.

One of the extremely important points Régis et al. raise is the question of what constitutes treatment failure in patients treated for VS with SRS. We are keenly aware of the important work done by the group in Marseille, as well as similar analysis performed by Dr. Pollock at Mayo Clinic regarding the transient tumor enlargement that is commonly seen in the first 6–12 months following SRS, and the sustained enlargement or regression that can occur.\textsuperscript{14,16} The editorial authors are concerned that we were perhaps overzealous in our declaration of SRS failure. They provide, in their editorial, 2 fascinating examples of patients who had significant tumor enlargement following SRS, followed by progressive tumor regression. In 1 case this did not happen until a decade after treatment, at which time the tumor had increased in volume approximately 9–10 times from the time of SRS! I don’t doubt that we would have been content to recommend continued observation of the first patient and would have been gratified by the regression, even though it was delayed. We emphasize this point in “Postradiosurgery Tumor Swelling,” in the Results section of our manuscript. Likewise, we would have emphatically recommended resection for the second patient after the patient returned after having been “lost to follow-up.” It is hard for us to attribute the delayed response in their second case to SRS performed more than a decade earlier, and we believe that a more plausible explanation is spontaneous tumor regression.\textsuperscript{10}

We, of course, think we are conservative in our estimation of SRS failure, especially because these were all patients treated by us. When we see sustained growth of ≥ 2 mm on 2 or more scans following SRS, we begin to be concerned that we don’t have tumor control. We have found operating on VSs following SRS to be more difficult compared with radiation-naïve tumors, as have other busy VS centers; therefore we are not inclined to enthusiastically push patients in that direction.\textsuperscript{7,8,11,22}

Many in the radiosurgical community only consider SRS failure when surgical intervention becomes “necessary.” Determining what necessary means may be quite different for different centers and for different patients. Thus, can a slowly growing small VS following SRS still be considered successfully treated? It raises the following questions. 1) Why treat in the first place, then? 2) Also, while waiting for the so-called delayed responder, how long should one wait? 3) Last, how large should the VS be allowed to grow before additional intervention is undertaken, especially if repeat SRS is going to be considered? We don’t believe that the stated goal of SRS for VS is to prevent the patient from undergoing microsurgery, but rather to halt the growth of the tumor; when that doesn’t occur, additional treatment should be considered (Fig. 1).

As also noted by Régis et al., we did not have good audiometric follow-up in this cohort of patients. Many of our patients do not live in Rochester, Minnesota, or within convenient driving distance to return for formal hearing analysis. Because of this referral network, we frequently rely on correspondence with the patient and local physicians to obtain audiograms. Often, this is not covered by insurance and patients cannot or will not pay for a follow-up hearing test. From their point of view, they either have useful hearing or they don’t. In a previous study we circumvented that problem by paying patients $60 to obtain an audiogram to ascertain long-term hearing outcome results and to forward it to us following SRS for VS performed using contemporary radiosurgical techniques.\textsuperscript{3} We showed hearing preservation rates of 48% at 5 years and 23% at 10 years in patients who had American Academy of Otolaryngology–Head and Neck Surgery (AAO-HNS) Class A or B hearing pre-SRS—results that were remarkably similar to other major centers with a significant experience treating...
Patients with smaller tumors and better hearing at the time of SRS did statistically better in terms of hearing preservation. This is exactly in keeping with the natural history studies in which patients who start with good hearing tend to keep good hearing on long-term follow-up with no intervention.

Régis et al. propose treating patients with SRS at diagnosis, hopefully when the hearing is still good, resulting in long-term tumor control and also hearing preservation. However, our just-referenced study, a prospective study comparing SRS and observation also previously alluded to, as well as the great majority of the literature, would argue that hearing continues to deteriorate following SRS, even with radiographic tumor control. A systematic review of the English-language literature by Yang et al., for instance, from the University of California, San Francisco, reported 4234 patients with a mean audiometric follow-up of almost 4 years. At a median of 35 months, only 51% of patients still had serviceable hearing. Perhaps one of the best pieces of evidence that SRS may not prevent future hearing loss in patients with VS comes from the Marseille group. In a very important study they reviewed 154 patients in whom serial audiometric data were obtained before and after SRS for VS. Of note, only pure tone average (0.5-, 1-, 2-, and 4-kHz) audiometric analysis was performed; unfortunately, no word recognition scores were provided. Looking at the whole group, patients were losing an average of 5.39 dB/year prior to SRS, which was reduced to 3.77 dB/year after SRS—not statistically significant. Even more important, for patients presenting with Class A hearing, prior to SRS their hearing trajectory was very stable, with an actual suggestion of improved hearing with observation (−0.57 dB/year), and post-SRS they developed hearing loss of 3.59 dB/year, which was highly significant (p = 0.007, Wilcoxon matched-pairs signed-rank test). The reader should be aware that the group at Haukeland University in Bergen, Norway, is currently conducting the first prospective, randomized study comparing observation and SRS in patients with VS (ClinicalTrials.gov Identifier: NCT02249572). Hopefully, the results of this study will help shed further light on this controversial topic.

Finally, to us, the questions our study and findings raise are as follows. 1) Should all new small- to medium-sized VSs be followed after diagnosis to better understand their growth patterns, to help elucidate the different tumor phenotypes before treatment is undertaken? 2) In a tumor...
growing rather fast (≥ 2.5 mm/year) is SRS still a reasonable first treatment, or should microsurgery be preferentially offered? 3) If SRS is performed for a fast-growing VS, should a higher marginal dose be considered? And finally, 4) does SRS bend the growth curve of a fast-growing VS, and therefore would a second treatment with SRS flatten or cause that curve to change to tumor regression?

Once again, we thank the editorial board of the Journal of Neurosurgery for allowing us to respond to the thoughtful and insightful comments and questions from Régis et al.

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