Editorial

Vestibular schwannomas

JACQUES J. MORCOS, M.D., F.R.C.S.(ENG), F.R.C.S.(ED)
Department of Neurosurgery, University of Miami, Florida

Radiosurgery is unquestionably a very attractive option in the treatment of vestibular schwannomas (VSs). Who can argue with the virtual absence of upfront morbidity or need for convalescence? In expert hands, it is standardized, precise, and reproducible. It does not erase the tumor but “controls” its growth, and that’s just good enough for most late-middle-aged and elderly patients with minimal symptoms and a reasonably small tumor. But the first tumor ever treated was only 40 years ago, and there has been a dearth of long-term series evaluating the durability of such treatment, an issue of immense importance for the younger patient particularly.

Is the tumor being simply “hypnotized” into a state of “dormancy,” only to awaken and grow at some later date? Is it true that if 3 years have passed after treatment with no visible tumor growth, one is then entitled to celebrate? Will hearing preservation be conserved over time? Will treatment be carcinogenic? Hasegawa et al.5 attempt to answer these and other questions in their article. They are to be commended for reporting on what is probably one of the largest Gamma Knife radiosurgical series for VSs and one with the longest follow-up. I will begin by summarizing their findings, and then I will offer a critique.

The authors retrospectively analyzed their consecutive series of VSs treated with single-fraction Gamma Knife surgery (GKS) during the period 1991–2000. They followed their patients over the long term, to an impressive median of 12.5 years. Of the original 451 patients, 440 were not lost to follow-up. Treatment was the primary therapy in 79%. Serviceable hearing was present in 77%. The median maximal and marginal doses were 25 Gy and 12.8 Gy, respectively, but a full one-third had marginal doses > 13 Gy, mostly in the earlier part of the series. The median volume treated was 2.8 cm³. Follow-up consisted of frequent MRI studies during the first 2 years and then annually thereafter. Radiographic change was assessed based on diameter, with a caliper-based threshold of 2 mm. Clinical change was determined, at least partially, through mailed questionnaires and reports from referring physicians. The progression-free survival (PFS) was assessed through censored Kaplan-Meier curves, and failure was defined by either tumor enlargement or the development of edema requiring surgery.

The general results were as follows. The mortality rate during follow-up was 8.6%, although 0.9% died directly due to their tumor/treatment. Follow-up MRI studies were available to review in 43% after 10 years and in 12% after 15 years. What was the fate of the treated tumors? Disappeared (referred to as complete remission by Hasegawa et al. [1%]), shrunk (partial remission [58%]), stable (34%), and enlarged (treatment failure [7%]). Interestingly, one-quarter of the “failures” occurred after 3 years. The PFS rate was 92% at 10 years overall, but 90% with the lower modern (< 13 Gy) marginal dose protocol. Multivariate analysis revealed the following factors to be harbingers of lower PFS: extent of tumor (Type D vs A, B, or C); marginal dose > 13 Gy; prior treatment; and female sex. The patients in whom GKS failed underwent craniotomies for the most part. In the remaining patients, a second GKS was performed, which failed 50% of the time, requiring a craniotomy.

The functional results were as follows. For cochlear function, hearing preservation drops steadily at 3, 5, and 8 years to 55%, 43%, and 34%, respectively, with worse results if the marginal dosage is > 13 Gy or if the initial Gardner-Robertson (GR) class is II (instead of Class I). Facial nerve morbidity is also dose-dependent: 4.9% if > 13 Gy, 1% if ≤ 13 Gy. Other complications included the following: delayed cyst formation (2.3%); malignant degeneration (0.3%); trigeminal neuralgia (1%); trigeminal neuropathy (2%); facial spasm (1.5%); and debilitating brainstem edema (0.7%).

This paper by Hasegawa et al. presents important data with respect to long-term outcome after GKS. It behooves us however to do a critical analysis, because these long-term data are not easy to replicate and will undoubtedly be relied on and quoted heavily by others. I would like to address several issues.

1) Patient Selection. We are told the demographics of the patient population but have no data whatsoever on the clinical profile. Was treatment indicated? Were patients symptomatic or was the tumor found incidentally? What is the relevant natural history against which we need to compare the outcomes described? Solid, reliable data from the Danish prospective database allow us to reach some important conclusions.10,11 The natural history of sporadic VS can be erratic and therefore unpredictable in the individual case. Tumors may enlarge, stabilize, shrink, plateau, and/or change their growth rates.

In the Danish patient cohort, with tumors measuring < 20 mm in extrameital diameter and followed conservatively, 83% of intrameital tumors remained stable. Of
Editorial

the 17% that grew, most grew during the 1st year after diagnosis, and progressively less thereafter, with none growing after 5 years. For the intrameatal-extrameatal tumors, 1% shrunk, 70% remained stable, and 29% grew. Again, of the 29% that grew, most did so in the 1st or 2nd year after diagnosis, and none grew after 5 years. Based on these growth data as well as data on the fate of hearing that will be discussed later, the Danish group recommended initial conservative follow-up for all tumors with extrameatal diameter < 20 mm, with periodic MRI studies up to 15 years, and then no further. Although their data showed no growth beyond 5 years, there were not enough patients followed beyond 10 years to offer statistical certainty.

In the current paper it is noteworthy that the median tumor size was 2.8 cm³, corresponding to a calculated estimated diameter of 1.75 cm. I too would suggest that a “wait and scan” policy for most small-to-medium tumors with minimal or no symptoms is probably the best policy. A summary of recent literature on this topic demonstrates that what may be considered failure of conservative management occurs in 9%–36% of cases. Spontaneous tumor regression can also clearly occur in as many as 19.4% of cases. In essence, GKS (or open surgery for that matter) may not explain favorable outcomes unless it demonstrably improves actuarial PFS and/or symptomatology. The data presented here do not allow us to reach a conclusion on this point and therefore must leave us in doubt as to what to credit for the great PFS results in smaller tumors; the natural history or the treatment.

2) Classifying Tumor Extent. These authors chose to categorize tumor extent into 4 classes: A (10%), B (54%), C (21%), and D (15%). Inconsistency is unfortunately the nemesis of classification schemes in the medical literature, making exact comparisons between different series impossible. A commonly used, well-established alternate system is the Hannover classification (T1, T2, T3a, T3b, T4a, T4b), and it appears to me that the best correspondence between the 2 schemes is as follows: A = T1; B = T2 and T3; C = T4a; D = T4b. This would make Group B quite a heterogeneous group that includes both small tumors with barely any extracanalicular extension and larger tumors that reach the pia mater of the brainstem. It would be interesting to see if, when subdivided further, Group B might yield some different outcomes.

3) Measuring Tumor Size. The authors have selected tumor volumes as the means to report tumor size (in cm³), but they also used a linear caliper method (used by others as well) to report change in size (in cm), with a threshold of 2 mm. How were the volumes computed? Was it through the GammaPlan software-based method at the time of treatment only? Was it based on the slice integration method from the MRI study? Was it estimated through the sphere approximation formula \( V = \frac{4}{3} \pi r^3 \) or through its simplified version \( V = \frac{d^3}{2} \)? Was the largest possible diameter used consistently to evaluate linear growth (or lack thereof)? How was the intracanalicular component handled? These are not trivial questions, because the methodology can affect results significantly.

There is a plethora of literature on this topic, but a recent publication demonstrates how inaccurate and unreliable the “single largest diameter” method is. With 25% retest errors, it can neither be reproduced accurately nor converted into volumetric data (particularly when small changes over time are expected). In another study looking at patients with neurofibromatosis Type 2 (NF2), volumetric semiautomated analysis was significantly more sensitive to tumor growth than the cubed linear diameter estimate. The latter method (linear) underestimated volume growth by 50%, and would have missed real growth on follow-up in 29% of lesions. If this limitation inherent to the linear methodology applies to the current study, as I suspect it does, then one has to wonder how different the PFS curves depicted in their Figs. 2 and 3 would have looked. I would welcome clarification from the authors.

4) Accuracy of Follow-Up Data. The strength of the paper of course is in the extended follow-up available. It would be important to know, though, to what extent questionnaires mailed to patients were relied on for data entry. What kind of self-assessment questions were asked of the patients and how subjective were the answers? One certainly hopes that facial nerve results for instance are not the “golden” period of 3 years post-GKS is not golden anymore. Of the 7% of patients in whom treatment failed, 26% showed tumor enlargement after 3 years. The message is clear. The patient is not off the hook at 3 years. Although the current data suggest that no patient experienced treatment failure after 10 years, it is conceivable that future longer and larger studies could still reveal failures beyond 10 years. Even though I am not suggesting extrapolating data from radiosurgical series of meningiomas, it is relevant to note that such delayed failures can occur after a prolonged quiescent period—14 years in some instances.

6) Is NF2 Different? The authors report no long-term progression in the 13 patients with NF2 who were enrolled in their study. This is quite surprising, given that traditionally VSs in patients with NF2 have been thought of and shown to be more aggressive lesions. For example, in a study of 30 such patients treated with GKS with similar dosing methodology, the actuarial tumor control rate steadily declined at 1, 2, and 5 years to 81%, 74%, and 66%, respectively. Only 33% of patients retained useful hearing at 5 years.

7) Predictors of PFS. Multivariate analysis uncovered the usual relevant variables—tumor extent; marginal dose; prior surgery; and, interestingly, female sex. Although “tumor extent” and “marginal dose” are independent, they did emerge as independent predictors. Generally, the larger the tumor the lower the marginal dose prescribed. At 10 years, PFS was significantly and expectedly lower (76%) for Group D tumors. Tumor volume incrementally influenced tumor progression: for every additional 1 cm³ of tumor, the hazard ratio increased by 1.12. Therefore, treatment failure after GKS is exponentially linked to linear tumor size.

The data presented also clearly show that marginal doses of > 13 Gy are certainly not justifiable anymore.