Acta Neurochirurgica (2019) 161:87–89
https://doi.org/10.1007/s00701-018-3742-2

EDITORIAL (BY INVITATION) - TUMOR - SCHWANNOMA

Treatment of small and medium-sized vestibular schwannoma—a need for better evidence

Morten Lund-Johansen [1,2]

Received: 13 November 2018 / Accepted: 16 November 2018 / Published online: 22 November 2018

Medical and surgical practice is based on experience gained through individual clinical experience as well as evidence gained through studies of various kinds. Obtaining experience may be challenging; many neurosurgical procedures require training past residency and many neurosurgical disorders such as vestibular schwannoma are indeed rare. Evidence is graded at levels depending on study design. The hierarchy of blinded, randomized, prospective, and retrospective non-randomized studies is well known. Case series and expert opinion represents less robust evidence, but these types of publications are very common in the medical/surgical literature. When performing a study, one needs to define valid and reliable endpoints. For example, an early postoperative MRI scan showing complete tumor removal may be reliable, but less valid if the patient became incapacitated postoperatively. Patient-reported data using a standardized questionnaire may be highly valid, but unreliable if the attending surgeon assists the patient in filling it out.

There is little high-class evidence to guide us about how to treat small and medium-sized vestibular schwannomas. Only a very small fraction of patients receives treatment while being enrolled into prospective comparative protocols. Instead, the vast body of literature consists of patient series receiving a single treatment presented by the caregiver. Despite the fact that many such publications adhere to internationally acclaimed guidelines on how to report outcomes, the risks of caregiver and patient selection biases are imminent [10]. In addition, VS patients are treated both by otosurgeons and by neurosurgeons. It has recently been shown that bias in publication practice may lead to the generation of so-called knowledge silos which hamper information being spread across specialties [15].

The three alternative treatments namely surgery, radiation, or observation are vastly different. The patients, who often seek advice from several doctors before they decide, acknowledge this. When we launched a randomized study some years ago, we allowed the patients to choose which treatment they wanted to pursue after hearing the risks and benefits of each active treatment option. The radiosurgery/microsurgery ratio at the end of enrollment was close to 2:1 [7]. Obviously, caregiver bias during patient counseling may influence treatment choice; if the health provider is in favor of one specific treatment, the patient is likely to choose that option. Thus, single-treatment series are common. For instance, some centers favor microsurgical resection of small tumors as the first alternative and report outcomes that are better than those reported after radiosurgery or observation.

The few studies that actually compare outcomes of VS treatment fail to reproduce the best outcomes presented in single-treatment series, whether it be after micro- or radiosurgery (see, e.g., [3, 12]). When we published our prospective comparative study, we found better outcomes for radiosurgery than microsurgery for facial nerve, hearing, and quality of life. The reviewers had diverse opinions about the study. Those who treated patients with radiosurgery were positive. On the other hand, we received criticism as some reviewers argued that our surgical outcomes did not match their own and thus were valid only to ourselves. Still, other comparative studies support our results and further indicate that, for instance, long-term hearing outcomes are best in observed and poorest in operated patients [17].

Operating on vestibular schwannoma is technically challenging and the experience of the surgeon is likely to affect the outcomes. In addition, the tumor's size, consistency, and adherence to critical adjacent neural and vascular structures make each operation quite unique. Due to the increasing number of caregivers who counsel patients about wait and scan

This article is part of the Topical Collection on *Tumor - Schwannoma*

✉ Morten Lund-Johansen
morten.lund-johansen@helse-bergen.no

[1] Department of Neurosurgery, Haukeland University Hospital, Bergen, Norway

[2] Institute of Clinical Science, Faculty of Medicine and Dentistry, University of Bergen, Bergen, Norway

followed by radiosurgery if the tumor grows, the number of cases operated each year may be low. This affects surgical training and experience. Our institution hosts the Norwegian national treatment facility for vestibular schwannoma. We receive 120–150 new referrals each year diagnosed among 5.5 million people but operate only about 25 of these, all typically relatively large (> 2.5 cm in posterior fossa diameter). The remaining either receive radiosurgery or observation until growth. Most future neurosurgeons are less likely to achieve surgical volumes similar to those of most of the few established experts.

Defining good endpoints for VS is difficult. When dealing with tumors, "cure" is a natural choice. Some microsurgeons argue that "cure" can only be achieved through complete removal of the tumor. Radiosurgery on the other hand, according to that philosophy, is not curative. The issue of "cure" may appear less relevant considering the quiescent nature of the tumor. The diagnosis of a small VS only very rarely becomes a severe threat to a person's health in developed countries. Patients treated with radiosurgery seem to maintain a stable quality of life and failure rates with documented progressive growth after radiation appear similar to the overall reported recurrence rates of operated patients [8, 13]. Within a group of patients with small- to medium-sized vestibular schwannomas receiving surgery, we have shown that complete tumor removal is associated with a higher quality of life compared to patients with subtotal resection especially as it relates to mental health subscales on multiple general quality of life measures [4]. However, careful patient counseling may take away some of the potential anxiety caused by the increasingly used concept of non-radical, neuroprotective surgery.

The concept of cure would appear more relevant if treatment leads to relief from present, or prevention of future, bothersome symptoms. As discussed above, this is uncertain. Patient-reported data can elucidate this. Together with colleagues at the Mayo Clinic, Rochester, MN, USA, we recently published a series of articles analyzing quality of life responses from 539 patients who were grouped according to single-treatment radiosurgery ($n = 247$), microsurgery ($n = 144$), or observation ($n = 148$). The mean follow-up time was 7.7 years. A control group of 103 non-tumor individuals responded to the same panel of questionnaires. The main finding of these studies is that vestibulocochlear complaints persist past treatment to a quite similar extent across treatment modalities. The group differences encountered suggested best outcomes for observation and poorest for surgery, but the difference between treatment groups was much smaller than the quality of life measured differences between vestibular schwannoma patients and non-tumor controls [1]. Our results are in agreement with another large series [14]. Thus, over time, patients may be less concerned about "cure" than about tumor-related symptoms. In 2006, we showed that the main driver of quality of life in VS patients was whether they had vertigo [9]. This appears to be a robust finding that has been confirmed by several others (see, e.g., [5]). Vertigo, dizziness, or "light-headedness" can only be measured by asking the patient. Unilateral hearing impairment on the other hand can be quantified exactly but seemed to be associated with quality of life to a lesser degree. Recently, we showed that even patients with bilateral grade A hearing scored significantly poorer on the Hearing Handicap Inventory than control individuals [16]. There may be discrepancy between what the patient perceives regarding their hearing and what can be measured on a formal audiogram.

The total removal of a small vestibular schwannoma while preserving hearing and facial function is undoubtedly a very good result, but the complaints of tinnitus and dizziness may persist. In the present issue of Acta, two expert groups report outcomes of microsurgery for small vestibular schwannoma and review selected literature [6, 18]. Both deal with retrospective case series showing the outcomes achieved by experienced surgeons. The outcomes are good. The authors refer to selected literature and indicate that microsurgery may be a preferred first a valid treatment alternative for small vestibular schwannoma. Both articles pay less attention to the outcomes reported in comparative studies.

Even if high-quality studies on VS are challenging to conduct, doctors treating vestibular schwannoma should strive towards the ideals of evidence-based medicine. There is undisputedly room for improving the level of evidence to guide us about how to treat VS, for reasons discussed above. Recent extensive reviews to provide comprehensive guidelines for the evaluation and management of vestibular schwannomas by our colleagues in the USA, and recently published in Neurosurgery, reveals all recommendations are based on level 3 evidence or worse [2, 11]. Our previous attempt to conduct a randomized study comparing surgery and radiosurgery failed and there are only a few prospective comparative studies. Key factors for study design are as follows: well-defined inclusion and exclusion criteria, independent blinded observers, and the use of standardized doctor, as well as patient-reported outcomes. Let us hope that long-term collaboration across institutions may increase the amount of valid and reliable data.

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