The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

Vestibular Schwannomas

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April 8, 2021
N Engl J Med 2021; 384:1335-1348
DOI: 10.1056/NEJMra2020394

Editors
Julie R. Ingelfinger, M.D., Editor

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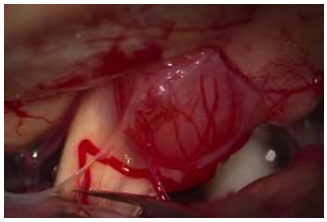
Introduction

Video



Microsurgical Resection of a Vestibular Schwannoma. (03:24)

VESTIBULAR schwannomas account for 8% of all intracranial tumors and are the most common neoplasm of the cerebellopontine angle in adults. These tumors derive from myelinating Schwann cells of the vestibular division of the vestibulocochlear (eighth cranial) nerve. The term "vestibular schwannoma" is preferred over the historical misnomer "acoustic neuroma." Though vestibular

evidence, plus several associated quality-of-life factors, render current management controversial. Furthermore, management varies substantially within the United States and globally.[2-4]

Several developments have transformed the diagnostic and therapeutic landscape of the disease. Widespread access to sensitive neurodiagnostic imaging has led to a notable rise in the detection of vestibular schwannomas[5,6]; an increasing proportion of cases are diagnosed, often incidentally, when the tumor is small and the patient is at an advanced age[6,7]; and there has been a shift toward conservative management strategies that prioritize preservation of neurologic function over cure.[8] This review focuses on sporadic unilateral vestibular schwannomas, which account for more than 95% of cases. Less commonly, vestibular schwannomas develop in the context of tumor-predisposing genetic disorders such as neurofibromatosis type 2 and schwannomatosis.[9,10]

Current Epidemiologic Features

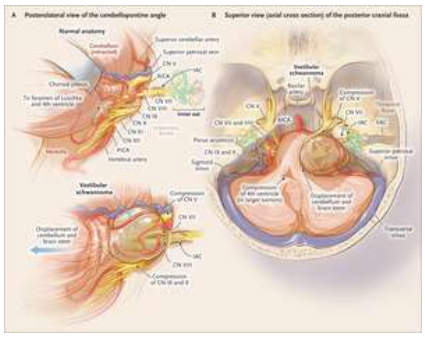
The observed increase in the incidence of vestibular schwannomas and the shifting demographic characteristics of affected patients are mainly due to greater access to enhanced diagnostics that increase detection, as opposed to a true biologic shift.[1,6,7,11] From the early 1900s through the 1970s, the incidence of vestibular schwannomas remained static, since patients presented with large tumors that had grown over a period of years without being detected.[12] From a historical incidence of 1 case per 100,000 person-years circa 1970, current incidence rates range from 3 to 5 cases per 100,000 person-years, with sustained increases even over the most recent decade.[6,7] This rise has been most dramatic among persons over the age of 70 years, for whom reported incidence rates now approach 20 cases per 100,000 person-years.[6] Today, cases are commonly diagnosed when patients are in the sixth or seventh decade of life, with tumors that are just millimeters in the greatest diameter.[6,7]

The inflection in disease incidence corresponds to increasingly widespread access to contrast-enhanced magnetic resonance imaging (MRI), along with more stringent adoption of screening protocols for asymmetric hearing loss. Analysis of prospective data from Denmark's national registry, spanning four decades, showed that the average age at diagnosis increased from 49 to 60 years, the mean tumor size decreased from 2.8 cm to 0.7 cm, and the severity of hearing loss at diagnosis was reduced.[7] Moreover, in regions with widespread access to MRI, population-based data suggest that up to 25% of all new cases are diagnosed incidentally during imaging that was obtained for unrelated indications (e.g., headache).[6] However, improved detection alone may not fully account for the increase in incidence witnessed in recent years.[11] Several groups have suggested that environmental exposures, such as cell phone use or long-term noise exposure may increase the risk of tumorigenesis; however, large case–control studies have failed to substantiate these associations.[13,14] Therefore, apart from exposure to ionizing radiation, there is no consensus on exposures that increase the risk of vestibular schwannoma.[15]

would have lived out their lives without having their tumors detected, are now receiving treatment.[1,16] Though the proportion of cases initially managed with a wait-and-scan strategy is higher than ever before, paradoxically, the total number of vestibular schwannomas per population that are treated with irradiation and microsurgery is probably greater today than in prior decades (see Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).[16] Nevertheless, a growing proportion of patients now undergo active monitoring of the tumor with serial imaging, signifying a transition in clinical care from up-front microsurgical resection, which epitomized treatment in earlier eras, to management of chronic disease.[1]

Disease Presentation

Figure 1.



Microanatomy and Structures Affected by Vestibular Schwannomas.

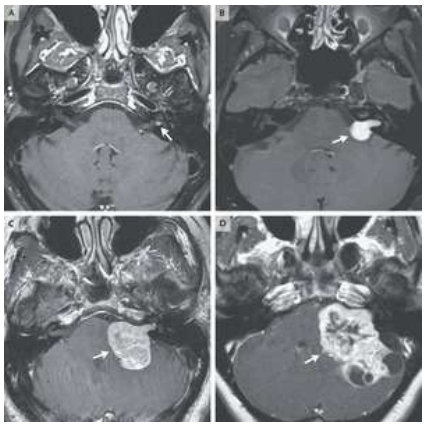
The spectrum of disease presentations, symptoms of progression, and treatment-associated morbidity are best understood in the context of the surrounding microanatomy (Figure 1). The most common presenting symptoms encompass ipsilateral sensorineural hearing loss in more than 90% of patients,[17] dizziness or imbalance in up to 61%,[17,18] and asymmetric tinnitus in 55%.[19] Hearing loss is often subtle initially and may first become apparent when the patient is using a telephone or lying in bed with the contralateral ear covered. Over time, many people have increasing difficulty with sound localization and speech comprehension in the presence of background noise, which results from the loss of binaural hearing. The character and severity of tinnitus vary. Tinnitus is thought to result from cochlear deafferentation and cortical maladaptation — a mechanism akin to deafferentation pain, as seen in the phantom limb syndrome.[20] Thus, even in cases of profound hearing loss or a severed cochlear nerve from microsurgery, tinnitus may persist. Though vestibular schwannomas arise from the vestibular nerves and objective loss of vestibular function is common on balance testing, symptoms of vertigo and continuous dizziness occur in only about 8% and 3% of cases, respectively.[18] This discrepancy presumably reflects the slow progression of vestibular loss associated with indolent tumor growth, which affords the opportunity for central

Patients with large tumors that compress the brain stem and cerebellum may have hypoesthesia in a trigeminal distribution, secondary trigeminal neuralgia, cerebellar dysmetria and ataxia, or slowly progressive hydrocephalus without alteration of consciousness. Even large tumors generally do not result in clinically apparent facial-nerve, trigeminal motor, or lower cranial-nerve dysfunction, although all these disorders may occur on occasion. If such findings are present, alternative diagnoses should be considered, such as schwannomas originating from other nerves (e.g., facial-nerve schwannoma), meningiomas, metastases from primary tumors at other sites, or malignant peripheral-nerve sheath tumors that develop new or secondarily within preexisting schwannomas, either spontaneously or after radiation treatment. In addition, several disease variants, including macrocystic and hemorrhagic vestibular schwannomas, may have a more aggressive course (Fig. S2).

There is a limited association between tumor size and the severity of hearing loss, tinnitus, or dizziness at diagnosis, and symptom progression is not strongly correlated with tumor growth.[17,21] These observations provide critical guidance for a wait-and-scan approach: worsening audiovestibular symptoms are not reliable barometers of tumor growth, and serial imaging studies should be obtained at regular intervals, regardless of symptoms. Furthermore, in contrast to symptoms related to mass effect in the posterior fossa, which often improve with tumor removal (e.g., trigeminal neuralgia), sensorineural hearing loss and vestibular hypofunction are not reversed with tumor treatment.[22]

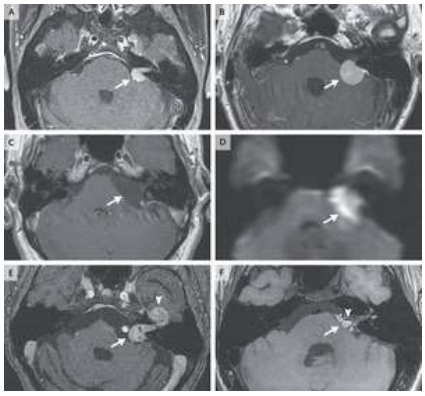
Diagnostic Evaluation

Figure 2.



Variations in the Size of Vestibular Schwannomas at Diagnosis.

Figure 3.



Radiographic Differential Diagnosis of Tumors of the Cerebellopontine Angle.

Thin-slice, gadolinium-enhanced MRI of the head is the standard diagnostic approach for the detection of vestibular schwannomas as small as 2 mm in diameter.[23] Features seen on imaging are highly sensitive and specific, resulting in an accurate radiologic diagnosis in most cases, without the need for a confirmatory biopsy (Figure 2 and Figure 3).[23,24]

The principal indications for obtaining a screening MRI study include sudden or asymmetric sensorineural hearing loss detected through pure-tone and speech audiometry.[19] With such a history, the probability of identifying a vestibular schwannoma is between 1% and 5%.[25,26] Though definitions of asymmetric sensorineural hearing loss vary, widely adopted protocols specify any interaural difference on pure-tone audiometry that is 10 dB or greater in two contiguous frequencies or 15 dB or greater in any single frequency (Fig. S3).[19] Although screening protocols for asymmetric sensorineural hearing loss have been widely adopted, the indications for performing MRI to investigate unilateral tinnitus or asymmetric vestibular dysfunction are not well defined.[19]

Patients with an isolated, unilateral vestibular schwannoma who do not have other signs of neurofibromatosis type 2 and have no affected relatives generally do not need to undergo genetic testing, nor do their family members (Text S1 in the Supplementary Appendix).[9] Neurofibromatosis type 2 is a rare autosomal dominant disorder caused by pathogenic variants within the NF2 gene; nearly half of affected people have a positive family history, and the remaining cases result from new variants.[9,10] Bilateral vestibular schwannomas develop in more than 90% of people with neurofibromatosis type 2, although other cranial and spinal schwannomas and meningiomas, spinal ependymomas, peripheral-nerve schwannomas, and ophthalmologic manifestations such as juvenile cataracts and retinal hamartomas may develop.[10]

Treatment

almost no risk of death.[27-29] Treatment strategies can be divided into an observational wait-and-scan approach, irradiation, microsurgery, and a combination of these methods. Several new drug therapies that aim to halt tumor growth, including aspirin and monoclonal antibodies, have recently been explored but remain investigational.[30] A list of ongoing clinical trials is summarized in Table S1. To date, there is no high-level evidence indicating that one treatment approach is unequivocally superior to others.[3,4] Instead, each strategy has a set of advantages and limitations.[3,31] Moreover, data show that the diagnosis itself and patient-related factors affect the quality of life more than does treatment choice.[32] Tumor size chiefly drives treatment recommendations; however, decision making is also guided by subtle patient- and provider-related factors.[2,33] Referral to a specialty center offers patients with a new diagnosis an opportunity to obtain information regarding tumor management and potential treatment of problematic symptoms. In view of the variations in clinical practice among centers, obtaining more than one opinion from larger specialty groups and obtaining educational material provided by independent, national patient-support organizations are encouraged.[2] Table S2 lists consensus statements, guidelines, and position papers published within the past 5 years.

WAIT-AND-SCAN APPROACH

The wait-and-scan approach has gained popularity for at least two reasons: many tumors are now discovered as small masses in older people with mild symptoms; furthermore, reports over the past 15 years have documented radiographically that only 22 to 48% of tumors have shown growth (most commonly defined as an increase of ≥2 mm in diameter) (Text S2) during a mean of 2.6 to 7.3 years of follow-up.[5-7,34-36] The most consistent predictor of future growth during an observational strategy is larger tumor size at diagnosis.[34-36] Typically, tumors that have a maximal diameter of less than 1.5 cm in the cerebellopontine angle are considered for a wait-and-scan approach.

Imaging and audiologic evaluation are commonly performed 6 months after the diagnostic MRI in order to identify a fast-growing tumor or a more aggressive process mimicking a vestibular schwannoma.[31] If there is no growth at 6 months, imaging and hearing assessments are performed annually thereafter until year 5, when many specialists advocate every-other-year assessments.[23,31] Given the unpredictable nature of tumor growth and the capacity for saltatory or delayed growth, lifelong follow-up is recommended.[31,37] If growth is definitively confirmed, most patients receive a recommendation to undergo radiosurgery or microsurgery. To minimize the cost of ongoing tumor surveillance and the risk of adverse events related to contrast material, several groups have transitioned to the use of thin-slice, heavily T2-weighted magnetic resonance cisternography without contrast material, which has a high degree of accuracy and interrater reliability.[24]

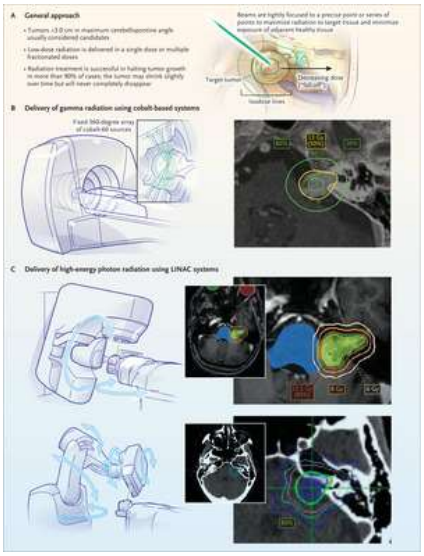
Progression of hearing loss, with or without radiographic evidence of tumor growth, is expected during observation with serial imaging.[38,39] The mechanisms driving hearing loss in patients with untreated tumors are incompletely understood but potentially include neurovascular compression of the cochlear

diagnosis, with a speech discrimination score of more than 70% (indicating that 70% percent of words were repeated back correctly by the patient), but after 10 years of observation, only 31% retained hearing above this threshold.[39] Notably, 88% of patients who started with a speech discrimination score of 100% still had a score of more than 70% at 10 years, suggesting that excellent speech comprehension at diagnosis portends favorable long-term hearing outcomes.

An important concern about an observational strategy is attrition. In a French study involving 386 patients, 16% were lost to follow-up in the first year of a wait-and-scan strategy.[41] Unfortunately, since symptom progression is not strongly correlated with tumor growth[21] and since the growth rate is highly variable, patients who are lost to follow-up are at increased risk for the development of a large tumor, with an associated increase in the risk of a poor outcome with eventual treatment.

RADIOSURGERY

Figure 4.



Radiosurgical Techniques for the Treatment of Vestibular Schwannomas.

Stereotactic radiosurgery typically involves the use of highly conformal radiation, defined as radiation delivered in 1 to 5 fractions to an image-defined target, with maximal sparing of the surrounding tissue. Gamma-knife radiosurgery is one type of conformal radiation. Gamma-knife treatment consists of 192 cobalt-60 sources arranged concentrically to deliver an ovoid isocenter of radiation. Treatment typically incorporates a stereotactic head frame and thin-slice, non–contrast-enhanced computed tomography and contrast-enhanced axial MRI to stereotactically target the tumor in three-dimensional space (Figure 4). Linear accelerator–based platforms are also used by many centers. Most of these systems involve a single, collimated radiation beam with a gantry that rotates around the patient, creating a focused arc of radiation that stereotactically targets the lesion of interest. Generally, the entire procedure is performed in an

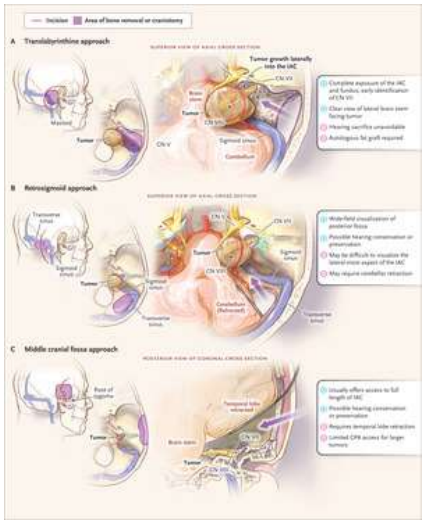
The aim of radiosurgery for a schwannoma is to prevent tumor growth; treatment does not confer a radiographic cure, and the tumor will be visible indefinitely on MRI. Transient tumor enlargement within the first 3 years after radiosurgery is common, although variable tumor shrinkage eventually occurs in more than half of treated cases.[42] After radiosurgery, patients undergo audiometric evaluation and MRI studies annually for the first 3 years, then every other year until 10 years, then every 5 years indefinitely.[31] In contemporary radiosurgery series, tumor control is reported in more than 90% of cases of vestibular schwannoma at 10 years of follow-up.[43] Radiosurgical treatment failure is typically defined by tumor growth that persists for more than 3 years, the development of signs or symptoms associated with progressive mass effect, and rapid tumor enlargement.[31] Salvage microsurgery is generally recommended after failed radiosurgery, although at several centers, repeat radiosurgery has been successful in select cases.[44]

Patients with tumors that have a maximal diameter of less than 3.0 cm in the cerebellopontine angle are usually considered to be candidates for radiosurgery. However, tumors that are less than 2.5 cm are preferred in order to minimize the risk of radiation-induced brain-stem edema, trigeminal neuropathy or neuralgia, and hydrocephalus, as well as diminished long-term tumor control.[45] Some centers preferentially use hypofractionation or conventional multifraction delivery of stereotactic radiation, which potentially allows for the treatment of larger tumors than those for which single-fraction treatment has traditionally been considered to be safe. Single-fraction stereotactic radiosurgery, with a marginal dose of 13 Gy or less, is associated with a 1% or lower risk of permanent facial-nerve weakness and less than a 5% risk of trigeminal neuropathy, depending on the tumor volume.[43] The risk of a secondary cancer from radiosurgery approaches 0.02%.[46] The influence of radiosurgery on progression of hearing loss remains controversial, but many centers report rates of serviceable hearing preservation of 50 to 70% over a follow-up period of 3 to 5 years.[38,47] Serviceable hearing designates a level of hearing that is still functionally useful, with or without a hearing aid, and is defined by a speech discrimination score of at least 50% and a pure-tone average threshold of 50 dB or less.[38]

MICROSURGERY

Microsurgical resection can be performed on tumors of all sizes and is the treatment of choice for large tumors associated with symptomatic brain-stem compression, hydrocephalus, trigeminal neuralgia or neuropathy, or a combination of these complications.[22,48] All procedures are performed while the patient is under general anesthesia and require the use of an operating microscope with intraoperative neural monitoring.[48,49] A narrated **video** outlining the steps involved in microsurgical resection of a vestibular schwannoma and the relevant anatomy can be viewed at NEJM.org.

Figure 5.



Microsurgical Approaches for the Treatment of Vestibular Schwannomas.

The three primary microsurgical approaches used to remove vestibular schwannomas are the middle fossa, translabyrinthine, and retrosigmoid approaches, each with benefits and limitations (Figure 5). The principal objectives are the same, regardless of the approach: maximal tumor removal with preservation of neurologic function. Intraoperative facial-nerve monitoring with electromyography is routinely used.[49] Cochlear-nerve monitoring is frequently used when hearing preservation is attempted, and monitoring of other regional cranial nerves may be incorporated for large tumors.[31,49] Most patients are hospitalized for 2 to 4 days after the procedure and are ambulatory at the time of discharge. Exertional activity is generally restricted for 6 to 12 weeks after surgery. Fatigue and ongoing imbalance are common during early convalescence but usually improve within 3 months. Most patients undergo a baseline postoperative MRI study within the first 12 months after surgery, with periodic surveillance MRI studies thereafter; the interval between studies is based on the extent of resection and the results of early postoperative imaging.[31] The risk of tumor recurrence after gross total resection is 0 to 2%.[28,50]

Primary surgical risks are directly proportional to tumor size and most often are related to postoperative hearing and facial-nerve function.[38,48] Serviceable hearing is preserved in 40 to 70% of patients with small tumors (<1.5 cm in diameter), and facial weakness is permanent in less than 10%.[27,38,51] The probability of preserving serviceable hearing after surgery for tumors that are more than 2.5 cm is less than 5%, and the risk of permanent partial or complete facial-nerve paralysis after total resection of large tumors is approximately 50%.[52-54] Given such risks, intentionally leaving a tumor remnant around the facial nerve and brain stem has gained popularity.[55] The risk of postoperative growth of residual tumor is proportional to the volume left behind.[31] Overall, approximately 30% of tumors regrow to some degree after subtotal tumor resection and are usually treated with radiosurgery.[31,56] Fortunately, the risk of other major neurovascular complications, such as permanent injury to other regional cranial nerves or perioperative stroke, is rare, even with large tumors.[29] The prevalence of postoperative cerebrospinal fluid leak is 9 to 13%,[57,58] aseptic meningitis 2 to 4%,[58,59] and culture-positive bacterial meningitis 1%.[59] Published data

Rehabilitation

In most people with vestibular schwannomas, long-term facial-nerve function remains good, and there is sufficient compensation for unilateral audiovestibular deficits. However, some patients require rehabilitative intervention — most commonly, those with long-term facial-nerve paralysis, bilateral hearing loss, or chronic dizziness or imbalance.

For people with vestibular schwannomas in whom serviceable hearing is maintained in the ipsilateral ear, observation (i.e., no additional hearing rehabilitation) or use of a conventional hearing aid is generally adequate. However, in most patients, nonserviceable hearing ultimately develops in the affected ear, resulting in impaired sound localization and difficulty understanding speech in the presence of background noise.[62,63] If aural rehabilitation is pursued, most available options encompass technologies that route sound from the deaf ear to the ear with better hearing through surgical means (i.e., bone-conduction implants) or nonsurgical means (e.g., contralateral routing of signals [CROS] hearing aids). Cochlear implantation to restore hearing in patients with sporadic vestibular schwannomas is currently investigational. Preliminary data suggest that 50 to 85% of highly selected patients with cochlear implants are able to understand speech. However, this strategy is feasible only in patients who have a cochlear nerve that has not been critically injured by microsurgery or radiosurgery (Fig. S4).[64,65] Despite the availability of these options, less than one third of people with vestibular schwannomas ultimately undergo trial use of a hearing device, and only approximately 20% regularly use such a device, in part because of the limitations surrounding these technologies but also because most people adequately adjust to the hearing deficit.[63]

Severe, chronic dizziness or imbalance, with an associated risk of falling, is rarely related to disease progression or tumor treatment and generally has a multifactorial cause.[18] Common conditions that may exacerbate dizziness include peripheral neuropathy, age-related loss of contralateral vestibular function, vision loss, and vestibular migraine.[18,66] Thus, people who report substantial dizziness or imbalance should undergo a comprehensive balance assessment to accurately identify any coexisting disorders and to assess and mitigate the risk of falling. The mammalian peripheral vestibular system has limited regenerative capacity. Thus, balance therapy is the therapeutic mainstay for people who have troublesome symptoms related to chronic vestibular hypofunction.[67]

Permanent facial-nerve paralysis is uncommon overall, but the risk approaches 50% among patients with large tumors who have undergone microsurgical resection.[53,54] Flaccid paralysis and eye dryness are primary concerns in the early postoperative period. Although many of the stigmata of facial-nerve injury can be electively managed, incomplete eye closure must be aggressively treated to reduce the risk of exposure keratopathy, commonly manifested as blurred vision, ocular pain, and redness. Eye lubricants and

considered if longer-term paralysis is anticipated or ophthalmologic complications appear. The rate and extent of facial-nerve recovery after microsurgery is variable. Improvement is generally greatest within 6 months after the onset of paralysis, but continued recovery can be seen for up to 18 months.[68] The management of permanent facial-nerve paralysis is complex and potentially time-sensitive. Therefore, referral to a specialty clinic should be considered for patients with severe facial-nerve paralysis who do not have improvement within the first 6 months.[68]

Conclusions

With increased access to sensitive neurodiagnostic imaging, the epidemiology and management of sporadic vestibular schwannomas have evolved substantially in recent years. Today, the diagnosis is often made when tumors are very small, as well as in older patients with minimal symptoms or incidentally. Treatment algorithms have evolved to prioritize functional outcomes over a definitive cure. Microsurgery is generally preferred for the treatment of tumors that are larger than 3 cm in diameter. However, in the absence of high-level evidence to inform decision making, there are multiple reasonable treatment options for most patients with small or medium-size vestibular schwannomas, including the wait-and-scan approach, radiosurgery, and microsurgery. As such, patient preference plays a major role in shared decision making.

Funding and Disclosures

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

Dr. Carlson reports receiving grant support from Cochlear Ltd. and holding pending patents 62/346,306, PCT/US2017/035617, and WO2017213978A1 on devices and methods for treating tinnitus with the use of electrical stimulation. No other potential conflict of interest relevant to this article was reported.

This article was updated on April 8, 2021, at NEJM.org.

We thank our colleagues, including Kelly D. Flemming, M.D., and John P. Marinelli, M.D., for editorial assistance with earlier versions of the manuscript, Andrew J. Goates, M.D., for editorial assistance with an earlier version of the narrated video, and Mohamed H. Khattab, M.D., Leslie A. Nussbaum, M.D., Ph.D., and Eric S. Nussbaum, M.D., for providing radiosurgery dose plans for Figure 4.

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Supplementary Material

Supplementary Appendix	PDF	11097KB
Disclosure Forms	PDF	238KB

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