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Modern Management of Acoustic Neuroma

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In Memoriam Prof. Robert Sedan

Prof. Robert Sedan, our mentor, was a creative mind and a humanist heart. He created in 1975 the Timone University Hospital Department of Functional and Stereotactic Neurosurgery. He created a series of new instruments for stereotaxis, including the side-cutting biopsy needle nowadays known under his name and commonly used for the vast majority of the stereotactic brain biopsies worldwide. He taught us the importance of multidisciplinary approach and team work.

His rich personality and legacy remain a permanent source of inspiration for his grateful fellows.

Jean Régis and Pierre-Hugues Roche, Marseille
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Vestibular schwannoma, a more modern update of the original medical term of acoustic neuroma, is a relatively rare and usually benign skull base tumor that has fascinated neurological surgeons for more than 100 years. Surgical pioneers such as Cushing advocated subtotal resection, whereas Dandy recommended complete excision. This set the tone for the sometimes controversial management of this tumor, which has continued to fascinate many generations of neurological surgeons, neuro-otologists, and more recently radiation oncologists. From surgical removal at all cost, evolved a strategy of cranial nerve preservation whenever possible. No tumor provides a greater test of a neurosurgeon’s or neuro-otologist’s skill than the acoustic neuroma, but the need for improved outcomes proved the driving force in the introduction of stereotactic radiosurgery as a potent management strategy. This volume should help the reader to understand the current spectrum of management strategies, and the enormous strides that have been made on patient’s behalves for better outcomes, preservation of cranial nerve function, and even improved quality of life – huge improvement beyond the early years of assessing outcomes by simply noting whether the patient survived or not. There are different operations that are appropriate for different patients. For patients who simply cannot ‘live’ with a tumor in their head, surgical extirpation should be attempted. For patients who are comfortable with the concept that minimally invasive radiosurgical strategy has a very high chance of achieving tumor dormancy and cranial nerve preservation, surgical removal is not necessary. This volume has taken several years to compile, and represents the current status of management of acoustic neuroma. Over the years, cranial nerve function rates have dramatically improved, and now hearing preservation is a reality.

L. Dade Lunsford, Pittsburgh, Pa.
Foreword

I am honored to be able to provide a foreword to this seminal book by Prof. Régis, who has assembled an excellent list of co-authors.

Acoustic neuroma, despite its relative rarity, continues to fascinate the neurosurgical, otologic, and now radiation oncologic community. Enormous strides have been made in the last two decades relative to enhanced long-term outcomes and reduction in patient morbidity.

History of Radiosurgery in Brief

Lars Leksell, the father of stereotactic radiosurgery, was the Swedish pioneer who was committed to what we now call minimally invasive treatment strategies to deal with difficult problems within the intracranial compartment. While his background was that of a neurophysiologist (who first described the gamma motor system), his training with Olivecrona in the 1930s convinced him that image guidance technology might be able to overcome the occasional operative disasters that he witnessed. His stereotactic fellowship was with the Philadelphia Temple University pioneers, Ernest Spiegel and Henry Wycis. By 1949 when he returned to Stockholm, Leksell had published his first article describing his arc-centered stereotactic guiding device. Two years later in 1951, he coined the term ‘stereotactic radiosurgery’ after combining his stereotactic guiding device with an orthovoltage dental X-ray unit. He first demonstrated the feasibility of the technique by irradiating the gasserian ganglion of 3 patients with trigeminal neuralgia. During the 1950s and 1960s, Leksell explored various alternative radiation delivery techniques. These ventures included cross-firing cyclotron generated protons in collaboration with Börje Larsson at the Gustav Werner Institute in Uppsala, a brief dalliance with the then emerging linear accelerator technology (which he found too unstable for radiosurgery based on the wobble of the gantry) and finally in 1967 the creation of a prototype 179 Cobalt-60 source Gamma Knife. This unit was placed in the Sophia Hospital in Stockholm. It was designed with slit collimators to create discoid-shaped lesions compatible with sectioning of the white matter tracts as required in functional neurosurgery. Its original Swedish name strålkniven or ‘the radiation knife’, evolved into ‘the Gamma Knife’. In 1975, a second prototype unit was developed equipped with circular collimators which created an oblate spheroidal dose profile. It was thereby more suitable for management of intracranial masses.
Leksell delegated various projects to his disciples at the Karolinska Institute where he had become Professor and Chair. The primary acoustic neuroma disciple was Dr. Georg Norén, who pioneered Gamma Knife acoustic neuroma radiosurgery. Georg applied his characteristic Swedish stoicism to withstand the cautious, somewhat skeptical, and always perfectionistic tendencies of Lars Leksell. The first patient was treated in 1969. Imaging was relegated to contrast encephalographic studies performed to outline the borders of the tumor using conventional X-rays. Dose planning was rudimentary, but Norén and Leksell pursued additional experience. It was their collaboration and dedication that now allows us to understand outcomes up to 37 years since the first patient underwent acoustic neuroma radiosurgery. Subsequent installations of additional prototype units in Buenos Aires, Argentina, and Sheffield, UK, ensued. The first efforts in North America were pursued by our group in Pittsburgh in 1987. The first patient treated (of our current 9000) had an acoustic neuroma. At that time, we were in the computed tomography era, and reasonably high resolution imaging was feasible, at least to define the extra-canalaricular component of the tumor. The new 1987 unit had 201 sources and an even larger collimator helmet (18 mm) was available.

Additional efforts began at other centers across the world, using modifications of linear accelerators, but the initial results from such technologies were not optimal. In part, this was related to a need for greater tumor conformality (the ability to confine the selected treatment to the 3-D volumetric tumor) and in part related to the unknown dosage thought necessary to control tumor growth. These doses were clearly too high, and in the early years were associated with transient facial weakness rates as high as 30–50%. Most centers began a gradual dose de-escalation strategy. At the same time, advances in neuroimaging such as the conversion to magnetic resonance imaging (MRI)-based planning, as well as the great improvements in dose planning facilitated by image integration and rapid computer processing, all contributed to improved outcomes. We recognized that small isocenters not only enhanced conformality, but greatly improved selectivity (the ability to restrict dose to surrounding tissue outside of the target volume). Tremendous improvement in patient outcomes followed earlier recognition of tumors when symptoms were less profound (mild hearing loss, unilateral tinnitus, mild imbalance, episodes of dizziness, etc). Such symptoms fostered early MRI scans as these imaging techniques became widely available. As the size of the tumors diminished at presentation, the need for minimally invasive treatment strategies continued to increase.

**The Goals of Radiosurgery**

The primary goal of radiosurgery is tumor growth control, a different concept than the traditional surgical goal of tumor removal, as verified by long-term postoperative imaging. After radiosurgery, the tumor looks the same at least initially; long-term control has to be verified with serial follow-up imaging studies. Eventually, we recognized that up to 70% of patients have tumor volumes that gradually regress over the course of 5–7 years. The secondary goal was to enhance neurological outcomes by preservation of first facial nerve function, and subsequently preservation of hearing when appropriate for patients whose hearing status was measurable at the time of the therapeutic option selection. In addition, of course, there are many other outcome measurements for acoustic neuromas such as return to work, reintegration to daily life, and minimization of neuropsychological sequelae of open surgery.

The rapid return to work possible after Gamma Knife radiosurgery and the long-term benefit have facilitated a major transformation in the delivery of patient care for acoustic neuroma patients. Several features have spurred growing interest in radiosurgery: an almost zero risk of facial weakness (a previously dreaded outcome...
because of its severe effect on personal perception of oneself and integration into the workforce), the opportunity to preserve hearing and the low risk of worsening balance disorders or exacerbating tinnitus. Both surgeons who perform radiosurgery and their patients have to be patient. Compared to microsurgical removal, there is no longer the before and after picture, now you see it, now you don’t. Instead, follow-up imaging reveals it is no longer growing, and often shrinks. Early growth of an acoustic neuroma (by a few millimeters) occurs in up to 3–5% of patients before the tumor settles down. In general, 98% of patients after radiosurgery have long-term tumor growth control. Shrinkage tends to develop over the course of time, but it is not necessary in most patients to maintain an adequate outcome. Hearing preservation rates at their preoperative level vary from 50 to 70% of patients. The rare patient may show improvement; however, 30–40% of patients show either hearing deterioration or even deafness over the course of time. Hearing preservation at 2 years after radiosurgery appears to be relatively long-lasting in a significant proportion of patients, although recent evidence suggests that between years 5 and 15, some patients will have further hearing deterioration even in the absence of tumor growth.

**Accomplishments of Stereotactic Radiosurgery**

Most providers can be confident about long-term tumor growth control outcomes in more than 98% of patients. In addition, we can maintain most neurological function in the vast majority of patients. By emphasizing high conformality and high selectivity, we can efficiently perform the procedure in a ‘wheels in to wheels out’ approach lasting only a few hours. The efficiency of the procedure has been greatly aided by a long-term commitment to using MRI (as an imaging technique to achieve high 3-D conformality) and to extremely rapid dose planning systems. We must continue to evaluate comparative technologies, including those that have been recently advocated to be able to deliver the beneficial effect using multiple sessions or stages. Ostensibly, such variations in technology and dose delivery are related to goals of enhanced neurological preservation. Unfortunately, from a statistical standpoint, in order to be able to see a 10% improvement in hearing preservation rates at 2 years, a prospective randomized trial with 1,000 patients in each arm might be necessary in order to be able to detect such a differential benefit between one technology and another. Although such a trial is obviously impractical and unlikely to occur, we continue to be assaulted by the claims of various vendors relative to the superiority of their technique. At present, no radiobiological or clinical data show the superiority of staged approaches to that of Gamma Knife radiosurgery.

We also know a great deal now about the radiobiological effect of radiosurgery and the pathological mechanism by which tumor growth control or even involution of the tumor occurs. Radiosurgery results in damage to individual tumor cells, perhaps dose dependent, which leads to the inability of tumor cells to go through mitosis. For slow-growth tumors that act like late-responding tissues, cells do not die until they attempt cell division. This may not occur for months or even years. Secondly, we also know that tumor blood vessel destruction enhances tumor control. This is verified by the striking response to radiosurgery identified on follow-up contrast-enhanced MRI studies. The high-dose areas of the tumor (e.g. 60–70% isodose) appear dark on MRI over several months. This helps to predict eventual shrinkage of the tumor over the course of additional years of observation.

**Further Efforts and Issues**

One of the major remaining issues has to do with the education of the appropriate providers of radiosurgery. In the United States, most centers
work in teams consisting of neurosurgeons, radiation oncologists, and medical physicists. Some centers also rely on the additional input from neuro-otologists with a special interest in the management of acoustic neuromas, as many of them are already the gatekeepers for diagnosis.

How do we continue to educate microsurgeons in the delicate skill of surgical removal, with an increasing percentage of the small tumors relegate to radiosurgery? Unfortunately, this trend means that when tumors are diagnosed in the 30- to 35-mm range, the patient will need microsurgical resection or at least significant tumor debulking.

At centers where neuro-otology provides significant input, should they be the primary providers of this technique? If so, what training and credentialing is required to be able to ensure their appropriate education? If non-neurosurgeons can do acoustic neuromas, can they not do petroclival meningiomas, pituitary tumors, or intracranial metastases? Both various professional societies as well as educational efforts must proceed to analyze this looming credentialing issue. Radiation oncologists need to have neuroanatomic-based radiosurgery as part of their clinical training. Virtually any academic site across the world should now have radiosurgical technologies capable of doing both intracranial, spinal and body radiosurgery.

Who will be the team leaders in these projects? Radiation oncologists bring a skill background in radiobiology education to the table, but do not generally have the same level of neurosurgical neuroanatomy in their background, and are certainly not familiar with the microsurgical options that can be offered as an alternative.

In general, fractionated radiation therapy techniques are rarely alternatives to radiosurgery.

Is the definition of radiosurgery changing? It appears to be evolving from Leksell's original concepts of a single procedure done with image guidance, to a procedure in which image guidance is used and coupled with various radiation techniques to deliver the dose in one or as many as five stages. This is not totally technology dependent, as the concept of stages has been applied not only by linear accelerator centers, but also by the Gamma Knife pioneer, Georg Norén himself, using the most current generation of the robotic Gamma Knife.

Can we really expect to achieve better outcomes by these techniques, and do we have measures actually to compare conformality and selectivity issues between technologies, followed by verifiable patient outcomes to show differences? Patients often become well educated relative to therapeutic options. Since they are the ones that either reap the benefit or pay the price, they are increasingly pro-active in order to obtain as much information as possible. Proper information is widely available. Some information on the internet is even true, but some is not. Patients need to make their own decisions based on adequate informed consent, but it is incumbent upon providers to be able to provide appropriate information over the course of time. In the United States, successful lawsuits have been paid based on incorrect, or frankly false or prejudicial information.

In the past, various largely erroneous pieces of information were told patients: (1) it causes cancer; (2) when it fails, it will be impossible to remove the tumor without major neurologic damage.

How have these issues been resolved? First, we know the theoretical possibility of delayed oncogenesis when radiation is delivered. Using radiosurgical principles, the volume of tissue in a single procedure that receives radiation is very low.

Is one radiation hit more or less risky than two hits? Opinions are divided on this particular issue. It seems, however, that we know of a few ‘numerator’ cases, perhaps five at the present time, in which new neoplasms within the radiosurgical field have been identified in follow-up of patients who underwent radiosurgery for acoustic neuroma. The ‘denominator’ is less well known, but assuming that 5 patients with acoustic neuromas fit this criteria (not treated by fractionated radiation), and 25,000 patients have had radiosurgery,
the empirical risk is 1/5,000. To put this into perspective, the risk of a major complication or death after surgical removal of an acoustic neuroma at centers of excellence is estimated to be between 1 in 200 to 1 in 500.

What about the outcomes of subsequent microsurgery for a patient who has had prior radiosurgery? This risk is hotly debated. There are those who feel that some tumors are more difficult to remove, and others (usually those with experience), who recognize that tumors in fact are often easier to remove because of the reduction in the number of blood vessels and central necrosis of the tumors. Of course, many patients with minimal growth of their tumor in the first year or two may never need to have anything done. Rarely should those patients be rushed to surgery under the pretense that their tumor is ‘growing.’ In the early days of radiosurgery, some patients were rushed to early surgery during the time of a maximal radiation reaction in the surrounding tissues (in the era of less conformity and poorer selectivity and higher doses), clearly not an optimal time to try to remove a tumor. With a little bit of patience (a virtue necessary for both acoustic tumor patients and their providers), most such tumors stabilize and subsequently regress, obviating the need for surgery. Less than 2% of patients require surgical intervention.

Can re-treatment be provided? In selected cases, repeat radiosurgery can be performed if a tumor shows defined growth, and the patient is considered to be a poor candidate for microsurgery or is unwilling to consider it. There are little data at the present time as to whether such patients have a greater risk of facial nerve weakness, or the outcomes in terms of vestibular or hearing function. Most patients who have had radiosurgery more than once represent a subgroup that first had microsurgery which failed, and subsequently required radiosurgery for different components of the tumor as it was shown to grow over additional years of observation.

More data from centers with a high volume are warranted. To date, we have very little evidence that various technological procedures are demonstrably superior. Hopefully, answers will come when the data is analyzed by centers with extensive experience, and by those that are not terribly afflicted by preconceived bias. Many of the questions and comments raised in this introduction will be elucidated in detail by the authors of the chapters of this book. Acoustic neuroma outcomes have been greatly improved by advances first in microsurgical techniques, and now by long-term outcome application of radiosurgery, which is appropriate, verifiable, and extremely clinically relevant treatment strategy. It is no longer an alternative. For most patients of a newly diagnosed acoustic neuroma in the era of high resolution imaging, radiosurgery represents the first-line management for these tumors. Over time, we need to establish whether there is any variation in technologies which further improve results, perhaps assess whether radiation protectors or radiation sensitizers are possible, understand more about the various treatment options for patients with bilateral tumors, and provide appropriate data that allow our patients to select a treatment strategy that is right for them. Our patients take the risks, and they reap the benefits.

L. Dade Lunsford, Pittsburgh, Pa.